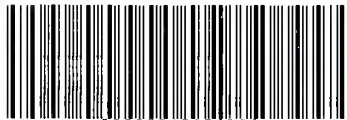


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RADIOLOGICAL, PHYSIOLOGICAL AND
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AND AFTER UTERINE ARTERY
EMBOLIZATION FOR FIBROIDS



Elizabeth Kagan Arleo

YALE UNIVERSITY

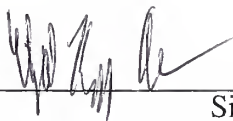
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**Radiological, Physiological and Psychosocial Variables Before and After
Uterine Artery Embolization for Fibroids**

A Thesis Submitted to the
Yale University School of Medicine
In Partial Fulfillment of the Requirements for the
Degree of Doctor of Medicine

by

Elizabeth Kagan Arleo

2004

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RADIOLOGICAL, PHYSIOLOGICAL AND PSYCHOSOCIAL VARIABLES BEFORE AND AFTER UTERINE ARTERY EMBOLIZATION FOR FIBROIDS.

Elizabeth Kagan Arleo, Michael G. Tal, and Robin M. Masheb. Vascular and Interventional Radiology Division, Department of Diagnostic Radiology, and Department of Psychiatry, Yale University School of Medicine, New Haven, CT.

Purpose: To investigate MRI-determined uterine and fibroid size and location, and fibroid-related symptoms, including quality of life and sexual function, in women with symptomatic fibroids before and after uterine artery embolization (UAE), as well as changing trends in gynecologists' opinion of the procedure.

Methods: Fifty-two women underwent pelvic MRI within four weeks of and six months post-procedure, from which uterine and fibroid size and location were noted. Women also completed a self-report questionnaire within four weeks before and one to six months after the procedure; the questionnaire investigated the frequency of fibroid-related symptoms, as well as quality of life and sexual function via the Short Form-36 (SF-36) and Female Sexual Function Index (FSFI). In addition, over a four year period, forty-two women completed a telephone survey in which each was asked about her gynecologist's initial opinion of UAE and about who initiated discussion of UAE.

Results: At baseline, women with symptomatic fibroids had worse quality of life and sexual function scores than healthy controls ($p < .05$). Pre-UAE, MRI-determined uterine and fibroid volumes were significantly correlated with urinary frequency/urgency ($p < .02$)

and some aspects of quality of life ($p<.04$), but not with other fibroid-related symptoms or sexual function. No significant differences with respect to fibroid-related symptoms were found between patients with or without subserosal or submucosal fibroids. After UAE, uterine and fibroid volumes significantly decreased ($p<.03$), as did urinary and pain symptoms ($p<.003$), as well as several aspects of quality of life ($p<.005$). In addition, more gynecologists had a favorable opinion of and were offering UAE than two years previously. ($p<.05$).

Conclusions: Women with symptomatic fibroids had impaired quality of life and sexual function, several aspects of which were correlated with uterine and fibroid volumes. Treatment with UAE, increasingly accepted by gynecologists, can significantly reduce uterine and fibroid volume and improve fibroid-related symptoms.

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I greatly appreciate the support of the Department of Diagnostic Radiology, as well as Dr. John N. Forrest, Jr., and the Office of Student Research, which enabled me to present the research detailed within this thesis at national meetings including the Society of Interventional Radiology (Salt Lake City, March 2003; Phoenix, March 2004), the American College of Obstetricians and Gynecologists (New Orleans, April 2003), the American Roentgen Ray Society (San Diego, May 2003), and the Radiological Society of North America (Chicago, December 2003).

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INTRODUCTION

“The available evidence on the management of uterine leiomyomata is of poor quality. Patients, clinicians, and policy makers do not have the data needed to make informed decisions about appropriate treatment. Given the prevalence of this condition and its substantial impact on women’s lives, obtaining these data should be a high research priority.”

-- Myers *et al.*, 2002 (1)

Uterine fibroids – also known as myoma, leiomyoma, and leiomyomata – are one of the most common conditions affecting women of reproductive age, with prevalence ranging from 20-77% (2). Thirty-five to fifty percent of women with fibroids are symptomatic, experiencing menorrhagia, pain (dysmenorrhea, dyspareunia), pressure-related symptoms (urinary frequency/urgency, constipation, bloating) and/or reproductive difficulties (infertility, miscarriage) (3). These benign tumors, which arise from the smooth muscle cells of the uterus, typically regress with menopausal decrease in steroid hormones. However, women taking hormone replacement therapy may continue to experience fibroid-related symptoms. The diagnosis of fibroids is made by history, pelvic/abdominal examination, and pelvic ultrasound or Magnetic Resonance Imaging (MRI).

Despite the prevalence of uterine fibroids and their considerable effect on women’s lives, and despite cell physiologic advances including the identification of 145 genes involved in fibroid growth and development (4), a recent systematic literature review concluded that there is little high-quality evidence with which to answer basic questions about fibroid treatment strategies (1). Therefore, the purpose of this research was to use quantitative MRI data and validated instruments to establish baseline radiological, physiological and psychosocial characteristics of premenopausal women

with symptomatic uterine fibroids and to follow these variables after treatment with uterine artery embolization (UAE), a relatively new procedure in the fibroid treatment armamentarium.

Fibroid-related symptoms

Although fibroids can cause a number of symptoms, exactly how they do so is unclear. One theory about the cause of bleeding symptoms is that fibroids may increase the number, but impede the function, of uterine blood vessels; another is that the presence of fibroids may impede the ability of the uterus to contract, thus causing inefficient expulsion of menstrual material or impairing the ability of uterine arteries to clamp down (5). The mass effect of fibroids (i.e., compressing the urinary bladder) is widely believed to be the mechanism by which fibroids cause urinary symptoms. However, anecdotal evidence from post-UAE patients that improvement in urinary symptoms precedes significant shrinkage in fibroid volume suggests that other mechanisms may play a role as well (6). The etiology of fibroid-related pain, including dysmenorrhea and dyspareunia, may be related to mass effect as well, or in some cases may be a side effect of attempted medical treatment (e.g., GnRH analogs, which may alter normal serum estrogen levels, can cause vaginal epithelial atrophy, decreased lubrication, and thus sexual pain).

In addition, fibroid-related symptoms are typically thought to be a function of size, location, and number of fibroids. In terms of size, the risk of fibroid-related symptoms, especially bleeding, is thought to increase with leiomyoma volume (7). In terms of location, menorrhagia has been attributed to intramural and submucosal fibroids,

whereas pelvic pain or pressure is more often attributed to intramural or subserosal fibroids (8). In terms of number of fibroids, the impact appears to be chronically undocumented, given that a recent systematic review of the literature on surgical and non-surgical management of fibroids found that 70% of studies on invasive treatments did not provide information on the number of leiomyomata (1).

The decision to treat symptomatic fibroids often is made based on uterine or fibroid size, or fibroid location, despite the fact that the relationship between these variables is not well established. For example, whereas it is known that the severity of endometriosis-related symptoms does not necessarily correlate with the amount (3) but does correlate with the location of endometriosis (9), it is not known whether the severity of fibroid-related symptoms necessarily correlates with uterine or fibroid size, or fibroid location within the uterus. This information is clinically relevant for the evidence-based treatment decision-making. The postulated association between submucosal fibroids and heavy bleeding (7), widely accepted clinically, often leads to hysteroscopic resection of fibroids located submucosally. Alternatively, a patient undergoing myomectomy or uterine artery embolization (UAE) may be counseled on the extent to which she may expect her fibroid-related symptoms to improve based on the location of her fibroids (10).

The first aim of this research, therefore, was to investigate the relationship between baseline MRI-determined total uterine volume, largest fibroid volume and fibroid location, and fibroid-related symptoms in premenopausal women with symptomatic uterine fibroids.

Quality of life and sexual function

The increased awareness of subjective well-being as a critical factor in health outcomes research has led to a proliferation of studies utilizing health-related quality-of-life (HRQOL) measures for assessing subjective well-being. HRQOL measures fall into two categories: disease/disorder-specific, or generic, such as the Medical Outcomes Study Short Form-36 Health Survey (SF-36) (11), a well-established generic HRQOL measure. However, to date, minimal data exists characterizing the quality of life, including sexual function, of women with leiomyomata by either method. Spies *et al* (12) developed a fibroid-specific version of the SF-36 and found that women with fibroids experienced lower health-related quality of life, as well as diminished sexual function, than normal controls, but to our knowledge, no generic HRQOL measure has been applied to establish baseline characteristics of women with fibroids alone.

A number of theories have been proposed to explain how fibroids cause sexual dysfunction. The mass effect theory suggests that uterine fibroids can have a direct mechanical influence on women's sexual function by making it difficult for the uterus to elevate and enlarge during arousal and contract during orgasm (13). It has also been hypothesized that fibroid-related vascular changes can have a direct effect on women's sexual function as well (i.e., vessels feeding fibroids "stealing" blood from pelvic organs) (14). In a paper on an animal model of vasculogenic female sexual dysfunction, Goldstein *et al* (15) reported that "vaginal engorgement and clitoral erectile insufficiency syndromes...exist when during sexual stimulation abnormal arterial circulation into the vagina or clitoris, usually from atherosclerotic vascular disease, interferes with normal vascular physiologic processes. Clinical symptoms may include delayed vaginal

engorgement, diminished vaginal lubrication, pain or discomfort with intercourse, diminished vaginal sensation, diminished vaginal orgasm, diminished clitoral sensation or diminished clitoral orgasm.” If fibroid neovascularization creates an abnormal arterial circulation into the vagina or clitoris, and/or a state of relative chronic ischemia of the pelvic organs, then this may be another possible mechanism by which fibroids cause sexual dysfunction.

Fibroids may also have an indirect biological influence on sexual function. Menorrhagia secondary to fibroids can cause iron-deficiency anemia, which may contribute to fatigue and thus negatively affect sexual desire. In addition, the side effects of medical therapies for fibroids, such as GnRH analogs, may alter normal serum estrogen levels, which can cause vaginal epithelial atrophy, decreased lubrication, and thus sexual pain. Fibroids may have an indirect psychological influence on sexual function as well. Abdominal enlargement secondary to fibroids may lead to detrimental changes in body- and self-image, feelings of being less attractive or sexy, and depression. Women may fear being rejected sexually, or conversely, worries about bulk, bladder and bowel dysfunction, or vaginal bleeding during intercourse may cause them to reject sexual activity. Reports from focus groups by Spies *et al* (12) corroborate both these possibilities: “Dissatisfaction with one’s appearance also had an impact on sexual function as some women in the focus groups “did not feel attractive”...[In addition, women stated that they] avoided sexual relations because of menorrhagia related to their leiomyomata.” Another hypothesis is that dyspareunia might lead a woman with fibroids to think that she has to endure pain with intercourse to satisfy her partner, or alternatively

may lead to avoidance of sexual activity. Failure to express these concerns to a partner may then cause difficulties in interpersonal relationships.

Given that fibroids can have profound direct and indirect biological and psychological influences on sexual function, and quality of life, the second aim of this research was to characterize the quality of life and sexual function of premenopausal women seeking interventional treatment for symptomatic uterine fibroids.

Fibroid treatment options

Historically, the treatment of fibroids has been surgical, with surgical treatment options including hysterectomy and myomectomy, and more recently, transvaginal resection of fibroids (16), endometrial ablation (17), laparoscopic-directed thermal coagulation (18), laser coagulation (19), cryotherapy (20), and MRI-guided focused ultrasound surgery (21). Hysterectomy is currently the most common surgical treatment for women with uterine fibroids, and fibroids are the number one discharge diagnosis for hysterectomy: of the estimated 600,000 hysterectomies performed annually in the United States, 40% are performed for fibroids (22). Myomectomy is the second most common surgical treatment for women with fibroids: an estimated 35,000 myomectomies are performed annually, including hysteroscopic myomectomies (to remove submucosal fibroids), laparoscopic myomectomies (to remove fibroids located serosally), and abdominal myomectomy (for fibroids in all locations) (23). However, since neither hysterectomy nor myomectomy is an ideal solution, nonsurgical treatments have been in high demand. Medical treatment options include GnRH analogs (24), gestriene (25), and low-dose mifepristone (26). However, many women are unresponsive to such medical

treatments or experience symptom recurrence after cessation of treatment (27). Given these limitations, UAE – first described as a treatment for fibroids by Ravina *et al* in 1995 (28), but utilized for twenty years preceding for the treatment of post-partum hemorrhage – has been increasing in popularity. To date, over 30,000 UAEs have been performed worldwide to treat fibroids (29).

Hysterectomy, myomectomy, and uterine artery embolization each have their advantages and disadvantages. In terms of overall success rates – defined as marked or complete resolution of fibroid-related symptoms, requiring no further treatment – there are notable differences: hysterectomy offers the advantage of complete cure by virtue of removing the fibroid uterus, in contrast to overall success rates of 75% for myomectomy (30) and 85-94% for UAE (31). Hysterectomy, however, is a major surgical procedure, involves several days of hospitalization and up to six weeks of convalescence, and results in permanent loss of the uterus and fertility. While myomectomy preserves the uterus, it is still major abdominal surgery associated with hospital and recovery times similar to hysterectomy, and with the potential for formation of painful, fertility-impairing abdominal adhesions. In contrast, UAE preserves the uterus, in the context of shorter hospital (<24 hours) and recovery times (1-2 weeks). Using ACOG's (American College of Obstetricians/Gynecologists) definitions for perioperative complications, the overall morbidity of UAE has been reported to be 5%, compared to an overall morbidity of 38.6% for myomectomies and 40.1% for hysterectomies (31). Furthermore, life-threatening events – defined as cardiopulmonary arrest, resuscitation, unplanned admission to an intensive care unit, or death – have been reported to occur in 0.5% of UAEs, in contrast to 1.5% of myomectomies and 1.0% of hysterectomies (31). However,

some reports have found that pregnancy after UAE may be complicated by higher rates of C-section, preterm labor, malpresentation, spontaneous abortion, and post-partum hemorrhage than normally occurs in the general population, which in part might be due to residual fibroids (32). On the other hand, Ornan *et al*, who studied the long-term sequelae of pelvic embolization for postpartum hemorrhage on fertility, found that all patients who desired to get pregnant were able to do so and experienced uncomplicated deliveries in the years after their embolization (33). Case series on pregnancy after myomectomy report rates of premature delivery and other complications to be similar to rates for the general population, however, the need for C-section necessarily increases if the uterine cavity was substantially entered during myomectomy (34).

The increased interest in UAE as a minimally invasive treatment option for fibroids has led to studies primarily assessing volume reduction and symptom relief. Most have used ultrasound, and quality of life and sexual function have been less well examined. For example, there have been case reports about sexual dysfunction after UAE (35), but no published studies prospectively assessing the effect of UAE on sexual function using validated measures. Therefore, the third aim of this research was to reevaluate total uterine volume and largest fibroid volume, as well as fibroid-related symptoms including quality of life and sexual function, after treatment with UAE using quantitative MRI data and two validated instruments.

Finally, given that gynecologists have traditionally been the providers of treatment for uterine fibroids (i.e., performing hysterectomy, myomectomy), the fourth aim of this research was to investigate patients' perceptions of their gynecologists' opinion of UAE.

Statement of purpose

In summary, the aim of this thesis was to test the following four hypotheses:

1. There is a relationship between baseline MRI-determined uterine and fibroid size and fibroid location within the uterus, and fibroid-related symptoms.
2. Women with symptomatic uterine fibroids have worse quality of life and sexual function than healthy women controls.
3. Following treatment with UAE, uterine and fibroid size decrease, and fibroid-related symptoms improve.
4. More gynecologists are expressing a favorable opinion of UAE and are offering UAE than two years earlier.

It is relevant to test these hypotheses given the prevalence of fibroids and the increasing role of radiology in fibroid diagnosis and treatment. The practical benefit is that data from this research will provide information for physicians and patients engaged in the fibroid-treatment decision-making process.

METHODS

Study design and subjects

The patient sample, prospectively accrued, consisted of premenopausal women undergoing UAE in the Department of Diagnostic Radiology, Vascular and Interventional Radiology Division, at Yale-New Haven Hospital. Patients were self-

referred or referred by gynecologists to the department for treatment. Exclusion criteria for the study were malignancy and postmenopausal status. Eligibility was not restricted by age, uterine or fibroid size, sexual orientation, or desire for fertility preservation. One-hundred and fifteen women had UAE performed by one of two hospital-based Interventional Radiologists (Michael G. Tal, MD, and Jeffrey Pollak, MD) from June 2001 through December 2003, and all women were offered the opportunity to participate in the study by either the Interventional Radiologist or his nurse practitioner. Fifty-two (45%) of these women chose to participate and completed the questionnaire prior to treatment with UAE. The same questionnaire was mailed (by the author) to these participating women after treatment with UAE, and thirty-seven (71%) returned follow-up questionnaires one to six months after the procedure. Hospital review board approval and patient informed consent were obtained.

Imaging

Following hospital UAE imaging protocol, women underwent pelvic MRI within four weeks of UAE and six months post-procedure. MRI was performed in the department utilizing a 1.5T scanner (General Electric, Signa, Milwaukee, WI) with a pelvic phased array coil. Following a gradient echo localizer sequence, sagittal STIR, axial T1 weighted SE, and axial and coronal FSE were obtained. Pre- and post-gadolinium scans were obtained in the sagittal plane to assess for myoma enhancement. The presence of submucosal fibroids, intramural fibroids with a submucosal component, intramural fibroids, subserosal fibroids with an intramural component, and subserosal fibroids were noted at baseline. Uterine dimensions were obtained from an axial image

via electronic cursor measurements of the mid corpus width and AP dimensions, and length was measured from a sagittal image from the top of the fundus (or fundal myoma if present) to the external os. Largest myoma diameter was obtained via cursor measurement from axial and sagittal images. Total uterine volume was calculated using the equation for the volume of an ellipse $[CC \times AP \times \text{transverse} \times .52]$, and largest fibroid volume was calculated using the equation for the volume of a sphere $[4/3\pi \times (\text{largest myoma diameter}/2)^3]$. MRI scans were read by residents and confirmed by attendings. Volume calculations were double-checked by the author.

Questionnaires

Demographic and fibroid-related questionnaires were created by Dr. Tal and Robin M. Masheb, PhD. In terms of demographic and clinical information, each patient was asked about her age, race, education, marital status, employment, and primary reason for seeking treatment. To assess fibroid-related symptoms, each patient was asked to rate the frequency of urinary symptoms (frequency/urgency, incontinence), pain (pelvic, abdominal, back), bleeding and bowel symptoms (constipation, diarrhea) that she experienced in the month prior to the survey on a scale of 0 (not at all), 1 (about one-fourth of the days in the past month), 2 (about one-half of the days in the past month), 3 (about three-fourths of the days in the past month) to 4 (every day in the past month).

In addition, each patient was asked to complete the following health-related quality of life and sexual function instruments, respectively:

1. Medical Outcomes Study Form Short-Form 36 (SF-36) Health Survey (1992)
(36): The SF-36 is a 36-item, state-of-the-art, self-report instrument to assess

health-related quality of life. The SF-36 has well-established reliability and validity, and was developed for use in the Medical Outcomes Study (37, 38). The scale includes eight domains known to be most directly affected by disease and treatment: physical functioning, social functioning, physical role limitation, emotional role limitation, bodily pain, general health, mental health, and vitality. SF-36 raw scale scores are transformed to t-scores (39). Higher scores reflect better functioning for all subscales.

2. Female Sexual Function Index (FSFI) (2000) (40): The 19-item FSFI has six subscales -- desire, arousal, lubrication, orgasm, satisfaction, and pain -- as well as an overall score. The questionnaire was developed as a multidimensional self-report instrument for assessing the key domains of sexual function in women. High test-retest reliability ($r=0.79$ to 0.86) and internal consistency (Cronbach's alpha values greater than and equal to 0.82), as well as construct and divergent validity have been reported. Individuals are asked questions such as how difficult it was to become lubricated ("wet") during sexual activity or intercourse over the past four weeks on a scale from extremely difficult, or impossible, to not difficult. Higher scores reflect better sexual functioning.

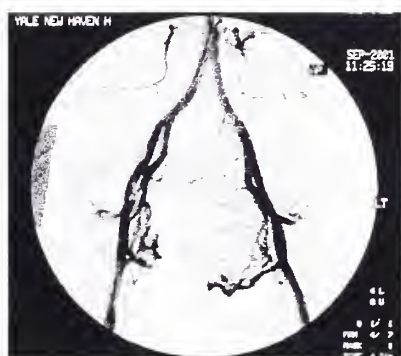
Uterine artery embolization

Bilateral selective uterine artery catheterization was performed with the use of fluoroscopic guidance. The catheter tips were placed within the transverse portion of the uterine arteries. Bilateral angiography was performed in order to identify the arterial anatomy and the branches feeding the fibroids. Five hundred to 710 micron polyvinyl

alcohol particles were then injected into each uterine artery until stasis or near stasis was achieved. Following embolization, a final arteriogram was obtained. Figure 1 shows pre- and post-embolization arteriograms for vasculature of a fibroid uterus. After the procedure, each patient was admitted overnight to the Interventional Radiology service for post-procedural pain management as needed.

Figure 1. a) Pre-embolization arteriogram of pelvic vasculature of a fibroid uterus. b) Post-embolization arteriogram of pelvic vasculature of a fibroid uterus.

a)



b)



Telephone survey

In order to investigate trends in gynecologists' opinions of UAE for fibroids, a telephone study was initiated in August 1998 to assess patients' perceptions of their gynecologists' opinion of the procedure. The surveys were administered to women undergoing UAE as above from August 1998 to July 2000 (by Dr. Tal) and from July 2000 to April 2002 (by the author). Twenty-one patients completed the survey during each time frame. Women were contacted chronologically, beginning with the first women to have UAE in each of the respective time frames; participating women represent the

first twenty-one women to be reached by telephone in each group. Each participant was asked to rate her perception of her gynecologist's initial opinion of UAE before the procedure on a scale from 1 (strongly opposed) to 6 (very favorable) or 7 (unaware of the procedure); whether the gynecologist offered UAE as a treatment option; whether she or the gynecologist initiated discussion of UAE; and whether she continued to see the same gynecologist after the procedure. In the second time frame, each participant was also asked whether she had Internet access at home and whether she used the Internet to learn about UAE.

Analysis

Data was analyzed using SPSS, version 10.0 (SPSS Inc, Chicago, IL) by the author and Dr. Masheb. Frequency and percentages were calculated for categorical variables, and means and standard deviations were calculated for continuous variables. Pearson product moment correlation coefficients were used to examine relationships among variables. Chi squares, t-tests, and ANOVAs were used to determine between-group differences.

Baseline quality of life and sexual function data were further analyzed using effect sizes to compare the present sample with normative samples. Effect sizes were determined by calculating the difference in scale scores between the UAE sample and the control samples, and dividing by the average deviation of the two samples. Effect sizes of 0.20, 0.50, and 0.80 or greater were considered small, medium, and large, respectively (41), and student *t* tests were calculated to determine the significance of the effect sizes. The control samples included a representative sample of the female general population

from the validation studies of the SF-36 (39) and a representative sample of healthy women from the original validation study of the FSFI (40).

Data from the telephone survey assessing changing trends in gynecologists' opinion of UAE were analyzed using Statcalc 1.1 (StatCalc Software, Etext.net publisher, Venice, CA). Frequency and percentiles were calculated for categorical variables. All reported p values were based on Fisher exact tests.

RESULTS

[N.B. The variation in N is a function of patients failing to answer all items on the questionnaires, and MRIs and MRI reports missing from the hospital file room and IDXRAD, the hospital computer radiology report system, respectively.]

Baseline Pre-UAE Data

The demographic and clinical characteristics of the participating women with symptomatic fibroids seeking UAE are displayed in Table 1. The mean patient age was 45 years (range 33-56). The majority (54%) of women were Caucasian; 40% were African-American, and 6% were Asian. Most women (59%) were highly educated, either holding a four-year college degree or a graduate degree or professional training. Women were more likely to be married or cohabiting or with a significant other (60%) than divorced, separated, widowed, or never married (40%). Women were mostly working full-time (78%), but 8% were unemployed.

Patients were asked about their primary reason for seeking treatment for their fibroids via a fill-in-the-blank question format. The majority of patients responded with more than one reason. Responses were then coded by the author into the following six categories: bleeding, pain, bulk, urinary, bowel symptoms, and dyspareunia. The most common reasons patients reported were bleeding (53%) and pain (51%). In addition, 31% self-reported bulk, 22% self-reported urinary symptoms, 4% self-reported bowel symptoms, and 4% reported dyspareunia as the primary reason for seeking fibroid treatment.

Table 1. Demographic and clinical characteristics of women with symptomatic fibroids seeking UAE

	Mean	SD
Age (N=52)	45.04	6.27
Total uterine volume (N=46)	841.69 cc	595.11 cc
Largest fibroid volume (N=46)	347.80 cc	352.47 cc
	N	%
Race (N=52)		
• Caucasian	28	53.8
• African American	21	40.4
• Asian	3	5.8
Education (N=51)		
• Less than high school graduate	1	2.0
• High school graduate	7	13.7
• Partial college or specialized training	13	25.5
• 4-year college graduate	14	27.5
• Graduate degree/professional training	16	31.4
Marital status (N=52)		
• Never married	9	17.3
• Married or cohabiting	28	53.8
• Significant other	3	5.8
• Divorced/separates	11	21.2
• Widowed	1	1.9
Employment status (N=49)		
• Working full-time (over 30 hrs/wk)	38	77.6
• Working part-time (less than 30 hrs/wk)	6	12.2
• Unemployed	4	8.2
• Student	1	2.0

Table 1 (continued)

Primary reasons for seeking treatment (N=49)*

• Urinary	11	22.4
• Pain	25	51.0
• Bleeding	26	53.1
• Bowel	2	4.1
• Bulk	15	30.6
• Dyspareunia	2	4.1

* Note: Does not total to 100% because many women reported more than one primary reason for treatment.

The mean total uterine volume pre-UAE was 842 cc (range 91-2870 cc) and the mean largest fibroid volume pre-UAE was 348 cc (range 1.44-1837.85 cc). Overall, 91% of women had intramural fibroids, 54% had subserosal fibroids, 30% had submucosal fibroids, 26% had intramural fibroids with a submucosal component, and 5% had subserosal fibroids with an intramural component (Table 2). The majority of women (74%) had fibroids in more than one location. Of the 26% with fibroids in one location, the most frequent location was intramural (82%).

Table 2. Fibroid locations in women with symptomatic fibroids seeking UAE (N=43)

Location	Present		Absent	
	N	%	N	%
Intramural	39	90.7	4	9.3
Subserosal	23	53.5	20	46.5
Submucosal	13	30.2	30	69.8
Intramural with submucosal component	11	25.6	32	74.4
Subserosal with intramural component	2	4.7	41	95.3

In terms of fibroid-related symptoms (Table 3), most women reported urinary frequency/urgency (81%), as well as pain (pelvic, abdominal, back) (81%) at least one-fourth of the days or more in the month prior to the survey. In addition, 56% of women reported bowel symptoms (constipation, diarrhea), and 33% reported bleeding at least

one-fourth of the days or more in the month prior to the survey. Furthermore, 48% of women reported urinary symptoms every day in the month prior to the survey.

Table 3. Frequency of fibroid-related symptoms in women with symptomatic fibroids seeking UAE (N=52)

Symptoms	Not at all		1/4 of days in past month		1/2 of days in past month		3/4 of days in past month		Everyday in past month		Totals: 1/4 of days or more	
	N	%	N	%	N	%	N	%	N	%	N	%
Urinary	10	19.2	8	15.4	6	11.5	3	5.8	25	48.1	42	80.8
Pain	10	19.2	15	28.8	9	17.3	9	17.3	9	17.3	42	80.8
Bleeding	35	67.3	6	11.5	5	9.6	2	3.8	4	7.7	17	32.7
Bowel	23	44.2	13	25.0	10	19.2	3	5.8	3	5.8	29	55.8

Table 4 contains the SF-36 means and standard deviations at baseline for the cohort of women with symptomatic fibroids pre-UAE and for the representative sample of the female general population from the validation studies of the SF-36 (39). In five of the eight quality of life subscales -- including physical role, bodily pain, general health, vitality, and social functioning -- the mean scores of women with symptomatic fibroids were significantly different than the mean scores of the female general population at the $p < .05$ level. In four of the five significant subscales, women with symptomatic fibroids reported worse health-related quality of life than the female general population, with effect sizes ranging from small to moderate. However, in terms of the general health subscale, women with fibroids reported better health-related quality of life than the female general population.

Table 4. Means, standard deviations, effect sizes, and paired t-tests for the SF-36 in women with symptomatic fibroids and U.S. female norms*

SF-36	Women with fibroids (N=46)		U.S. female norms* (N=1412)		Effect size**		t	p
	Mean	SD	Mean	SD	Quantitative	Qualitative		
Physical functioning	76.9	25.0	81.5	24.6	-0.19	ns	-1.24	ns
Physical role	65.7	39.1	77.8	36.2	-0.32	Small	-2.07	<. 025
Bodily pain	64.4	25.6	73.6	24.3	-0.37	Small-moderate	-2.40	<. 01
General health	80.0	14.1	70.6	21.5	0.53	Moderate	4.38	<. 005
Vitality	48.3	25.3	58.4	21.5	-0.43	Small-moderate	-2.68	<. 005
Social functioning	75.2	24.8	81.5	23.7	-0.26	Small	-1.71	<. 05
Emotional role	74.8	38.1	79.5	34.4	-0.13	ns	-0.82	ns
Mental health	69.6	20.0	73.3	18.7	-0.19	ns	-1.23	ns

* Sample from the National Survey of Functional Health Status (Ware *et al.*, 1993) (39).

** Effect sizes of 0.20, 0.50, and 0.80 or greater are considered small, moderate and large, respectively (Kazis *et al.*, 1989) (41).

ns = not significant.

Higher scores reflect better health-related quality of life.

Table 5 contains the FSFI means and standard deviations at baseline for the cohort of women with symptomatic fibroids pre-UAE and for the representative sample of healthy women from the original validation study of the FSFI (40). In all sexual function subscales – including desire, arousal, lubrication, orgasm, satisfaction and pain - and the overall score, the mean scores of women with symptomatic fibroids were significantly different than the mean scores of healthy women controls at the $p < .005$ level. Women with symptomatic fibroids reported worse sexual function than healthy women controls, with effect sizes ranging from small to moderate.

Table 5. Means, standard deviations, effect sizes, and paired t-tests for the FSFI in women with symptomatic fibroids and healthy women without sexual dysfunction*

FSFI	Women with Fibroids (N=46)		Healthy women w/o sexual dysfunction (N=131)*		Effect size**		t	p
	Mean	SD	Mean	SD	Quantitative	Qualitative		
Desire	5.7	2.0	6.9	2.4	-.54	Moderate	-3.56	<. 005
Arousal	12.6	6.2	16.8	7.0	-.64	Moderate	-4.39	<. 005
Lubrication	14.5	6.7	18.6	7.5	-.58	Moderate	-4.02	<. 005
Orgasm	10.7	4.9	12.7	5.4	-.39	Small-moderate	-2.60	<. 005
Satisfaction	10.6	4.6	12.8	5.0	-.47	Small-moderate	-3.11	<. 005
Pain	10.1	5.3	13.9	6.2	-.66	Moderate	-4.60	<. 005
Overall score	24.1	9.5	30.5	10.7	-.63	Moderate	-4.34	<. 005

* Sample from Rosen *et al.*, 2000 (40).

** Effect sizes of 0.20, 0.50, and 0.80 or greater are considered small, moderate and large, respectively (Kazis *et al.*, 1989) (41).

Higher scores reflect better sexual functioning.

Table 6 displays the correlations between the frequency of fibroid-related symptoms and MRI-determined total uterine volume and largest fibroid volume at baseline. Urinary frequency/urgency was significantly correlated with total uterine volume and largest fibroid volume ($r=.37$, $p=.01$ and $r=.35$, $p=.02$, respectively), such that greater frequency of urinary symptoms is related to larger uterine and fibroid volumes.

Table 6. Correlations between fibroid-related symptoms and MRI-determined total uterine volume and largest fibroid volume at baseline (N=46)

Symptoms	Total uterine volume		Largest fibroid volume	
	r	p	r	p
Urinary	.37	.01*	.35	.02*
Pain	-.28	.06	-.28	.06
Bleeding	-.13	.40	-.27	.07
Bowel	-.19	.21	-.28	.06

Table 7 displays the correlations between SF-36-determined quality of life and MRI-determined total uterine volume and largest fibroid volume at baseline. Physical

function and general health were significantly correlated with total uterine volume ($p=.04$ in both cases respectively). Bodily pain was significantly correlated with largest fibroid volume ($p=.02$).

Table 7. Correlations between SF-36-determined quality of life and MRI-determined total uterine volume and largest fibroid volume at baseline (N=46)

SF-36 scales	Total uterine volume		Largest fibroid volume	
	r	p	r	p
Physical function	.32	.04*	.25	.11
Physical role	.08	.63	.11	.48
Bodily pain	.20	.19	.35	.02*
General health	.31	.04*	.23	.15
Vitality	.25	.11	.29	.06
Social function	.21	.17	.22	.15
Emotional role	-.07	.66	.06	.71
Mental health	.13	.41	.03	.84

Table 8 displays the correlations between FSFI-determined sexual function and MRI-determined total uterine volume and largest fibroid volume at baseline. None of the FSFI scales – including desire, arousal, lubrication, orgasm, satisfaction, pain or overall score – were significantly correlated with either total uterine volume or largest fibroid volume.

Table 8. Correlations between FSFI-determined sexual function and MRI-determined total uterine volume and largest fibroid volume at baseline (N=46)

FSFI scales	Total uterine volume		Largest fibroid volume	
	r	p	r	p
Desire	.19	.23	.00	1.00
Arousal	.04	.82	.03	.83
Lubrication	-.02	.89	-.12	.91
Orgasm	-.02	.90	-.01	.95
Satisfaction	.03	.87	.02	.88
Pain	.05	.77	.07	.65
Overall score	.04	.81	.02	.89

In order to investigate whether fibroid location had any effect on fibroid-related

symptoms, ANOVAs were performed to test for between-group differences based on presence or absence of fibroids in each of two locations. Subserosal and submucosal fibroids were chosen because they provided relatively discrete, non-overlapping groups (i.e., subserosal fibroids were present in roughly half the women (53%) and absent in roughly half the women (47%); the groups with respect to submucosal fibroids were less equal in size – 70% (present) and 30% (absent); analysis was not run on intramural fibroids because the two groups – those with intramural fibroids present (91%) and those with submucosal fibroids absent (9%) – because of insufficient power). No significant differences with respect to fibroid-related symptoms were found between patients with and patients without subserosal fibroids (Table 9).

Table 9. Comparison of fibroid-related symptoms in patients with and without subserosal fibroids (SSF) using ANOVA

	Presence of SSF (N=23)		Absence of SSF (N=20)		F	p
	Mean	SD	Mean	SD		
Urinary	2.43	1.73	2.25	1.74	.12	.73
Pain	1.65	1.34	1.75	1.41	.06	.82
Bleeding	.61	1.12	.70	1.30	.06	.81
Bowel	.74	1.10	1.15	1.35	1.21	.28

No significant differences with respect to fibroid-related symptoms were found between patients with and patients without submucosal fibroids (Table 10).

Table 10. Comparison of fibroid-related symptoms in patients with and without submucosal fibroids (SMF) using ANOVA

	Presence of SMF (N=13)		Absence of SMF (N=30)		F	p
	Mean	SD	Mean	SD		
Urinary	2.23	1.64	2.40	1.77	.09	.78
Pain	1.38	1.26	1.83	1.39	1.00	.32
Bleeding	.85	1.34	.57	1.14	.49	.49
Bowel	.92	1.19	.93	1.26	.00	.98

Post-UAE Data

Thirty-seven patients (71%) completed follow-up questionnaires between one and six months post UAE. The questionnaires were identical to the baseline questionnaires. The baseline and follow-up groups were not significantly different with respect to age ($F(1,X)=.85$, $p=.36$), race [$X^2(1)=0.97$, $p=.32$], education [$X^2(1)=1.01$, $p=.32$], or employment [$X^2(1)=0.18$, $p=.67$]. The baseline and follow-up groups differed with respect to marital status [$X^2(1)=5.11$, $p=.02$], such that significantly more married or cohabiting women participated in the follow-up than did in the baseline survey.

Seventeen patients (37%) of the baseline sample for which MRI data was available ($N=46$) have completed follow-up MRIs six months post UAE as this thesis goes to print. Total uterine and largest fibroid mean volumes at baseline and at six months post-UAE are displayed in Table 11, with p values based on t-tests. Mean total uterine volume six months post-UAE was 493 cc (range, 100-1304 cc), with a 41% volume reduction from baseline. Mean largest fibroid volume six months post-UAE was 228 cc (range 2-1150 cc), with a 35% volume reduction from baseline.

Table 11. Means, standard deviations, and paired t-tests for total uterine volume and largest fibroid volume at baseline and six months after-UAE

	Baseline (N=46)		6 months post-UAE (N=17)			
	Mean	SD	Mean	SD	t	p
Total uterine volume	841.69	595.11	492.95	366.27	2.73	.02*
Largest fibroid volume	347.80	352.47	227.54	274.48	2.46	.03*

In terms of frequency of fibroid-related symptoms post-UAE (Table 12), 49% of women reported no urinary frequency/urgency, 54% reported no pain, 70% reported no

bleeding difficulties, and 50% reported no bowel problems in the month prior to survey. Furthermore, patients reported significantly less urinary frequency/urgency post-UAE than at pretreatment ($F(1,36)=16.59$, $p<.001$), with a 54% decrease in urinary symptoms (Table 13). Patients also reported significantly less pain post-UAE than at pretreatment ($F(1,36)=9.37$, $p=.003$), with a 49% decrease in pain symptoms.

Table 12. Frequency of fibroid-related symptoms after UAE (N=37)

Symptoms	Not at all		1/4 of days in past month		1/2 of days in past month		3/4 of days in past month		Everyday in past month		Totals: 1/4 of days or more	
	N	%	N	%	N	%	N	%	N	%	N	%
Urinary	18	48.6	6	16.2	6	16.2	4	10.8	3	8.1	19	51.4
Pain	20	54.1	8	21.6	4	10.8	1	2.7	4	10.8	17	45.9
Bleeding	26	70.3	8	21.6	2	5.4	0	0	1	2.7	11	29.7
Bowel	18	50.0	12	33.3	2	5.6	3	8.3	1	2.8	19	51.4

Table 13. Univariate analysis of fibroid-related symptoms before and after UAE

Symptom	Pre-UAE (N=52)		Post-UAE (N=37)		F	p
	Mean	SD	Mean	SD		
Urinary	2.48	1.65	1.14	1.36	16.59	.000*
Pain	1.85	1.39	.95	1.33	9.37	.003*
Bleeding	.73	1.25	.43	.83	1.59	.211
Bowel	1.04	1.19	.81	1.06	.89	.348

Higher scores reflect worse symptoms (Symptoms scale: 4 = experienced the given symptom every single day in the month prior to survey; 3 = experienced the given symptom three-fourths of days in the month prior to survey; 2 = experienced the given symptom half the days in the month prior to survey; 1 = experienced the given symptom one-fourth of the days in the month prior to survey; 0 = did not experienced the given symptom at all in the month prior to survey)

In terms of quality of life, women reported significantly better physical function post-UAE than at pretreatment ($F(1,36)=8.11$, $p=.005$), with a 22% improvement in physical function (Table 14). Women also reported significantly better quality of life with respect to bodily pain post-UAE than at pretreatment ($F(1,36)=10.07$, $p=.002$), with a 26% improvement in bodily pain. The physical component summary scores of the SF-36 were also higher post-UAE than at pretreatment ($F(1,36)=8.13$, $p=.006$), with a 13%

improvement (with higher scores reflecting better quality of life).

Table 14. Univariate analysis of SF-36-determined quality of life before and after UAE

SF-36 scales	Pre-UAE (N=52)		Post-UAE (N=37)		F	p
	Mean	SD	Mean	SD		
Physical function	77.4	26.0	94.2	28.6	8.11	.005*
Role physical	66.8	38.2	77.0	31.9	1.76	.188
Bodily pain	64.2	25.0	80.6	22.6	10.07	.002*
General health	80.1	14.1	82.3	16.5	.43	.516
Vitality	49.1	24.6	53.9	23.3	.81	.370
Social function	76.4	24.1	84.4	19.9	2.68	.106
Role emotional	78.0	36.6	84.7	32.0	.81	.370
Mental health	70.9	19.7	74.1	16.2	.60	.440
Physical component summary score	47.19	9.34	53.24	9.36	8.13	.006*
Mental component summary score	47.94	10.41	48.83	9.20	.16	.70

Higher scores reflect better quality of life.

Post UAE, women's reported sexual function was not significantly different than at pretreatment in any respect, including desire, arousal, lubrication, orgasm, satisfaction, pain, or the overall score.

Table 15. Univariate analysis of FSFI-determined sexual function before and after

FSFI scales	Pre-UAE (N=52)		Post-UAE (N=37)		F	p
	Mean	SD	Mean	SD		
Desire	5.67	1.87	5.97	2.05	.48	.492
Arousal	12.51	6.11	10.67	7.61	1.53	.220
Lubrication	14.44	6.70	11.27	8.95	3.46	.066
Orgasm	10.45	4.95	8.34	6.29	2.90	.092
Satisfaction	10.37	4.41	9.10	5.54	1.28	.262
Pain	9.83	5.19	8.15	6.87	1.63	.205
Overall Score	23.75	9.38	20.45	12.67	1.81	.182

Higher scores reflect better sexual function.

Changing Trends in Gynecologists' Opinions of UAE

Table 16 contains the results of the telephone surveys administered during the two time frames. The two survey groups were quite similar. The mean patient ages were 45 years in the first survey time frame and 44 years in the second. Seventy-five percent of respondents to the first survey and 73% of respondents to the second survey had earned at least a 4-year college degree (differences not statistically significant, Fisher exact test, $p>.05$).

According to patients' perceptions, there was a significant difference in the number of gynecologists initially opposed to UAE ($p<.05$), with fewer gynecologists initially opposed to UAE in the second survey in comparison with the first. There was also a significant difference in the number of gynecologists who offered UAE as a treatment option ($p<.05$), with more gynecologists offering UAE as a treatment option in the second survey in comparison with the first. In addition, as reported by patients, there was a significant difference in the number of gynecologists who initiated discussion of UAE with their patients in the second survey in comparison with the first. Finally, there was no significant difference in the percentage of patients who did not return to gynecologists perceived by their patients to be initially opposed to UAE when comparing the two surveys.

Table 16: Changing trends in patients' perceptions of gynecologists' opinions of UAE: telephone survey results

	Time Period				
	August 1998 to July 2000		July 2000 to April 2002		
	Frequency	Percent	Frequency	Percent	p
No. of respondents	21/50	42%	21/39	54%	
Gynecologists initially opposed to UAE	16/21	76%	7/21	33%	<.05
Gynecologists who offered UAE as a option	1/21	5%	8/21	38%	<.05
Gynecologists who initiated discussion of UAE	2/21	10%	9/21	43%	<.05
Patients who didn't return to gynecologists initially opposed to UAE	8/9	89%	5/7	71%	Ns

Ns = not significant

Participants in the second survey were also queried regarding availability of Internet at home and whether they used it to learn about UAE. Seventy-one percent (15/21) reported they had Internet access at home, and 62% (13/21) reported that they used the Internet to learn about UAE.

DISCUSSION

The purpose of this research was to use quantitative MRI data and validated instruments to establish baseline radiological, physiological and psychosocial

characteristics of premenopausal women with symptomatic uterine fibroids and to follow these variables after treatment with UAE. This research represents the largest systematic examination of patients undergoing uterine artery embolization for fibroids to date at Yale-New Haven Hospital, Department of Diagnostic Radiology, Vascular and Interventional Radiology Division. The design of the research has several strengths. First, we used MRI to characterize the relationship between uterine and fibroid size and fibroid position within the uterus, and fibroid-related symptoms, including quality of life and sexual function, which has not been done previously. Second, in terms of quality of life and sexual function, we used two empirically validated and reliable questionnaires, the SF-36 and the FSFI, to report baseline characteristics of women with symptomatic fibroids seeking UAE and compared them to controls to understand these women relative to norms.

Baseline Data

The first hypothesis of this study was that there is a relationship between baseline uterine and fibroid size and fibroid position within the uterus, and baseline fibroid-related symptoms – and we sought to define more specifically the nature of this relationship. We also hypothesized that women with symptomatic uterine fibroids have worse quality of life and sexual function than healthy women controls – and we sought to define more specifically the severity of the dysfunction.

The baseline characteristics of the women participating in our study are similar to the results of the largest multi-center prospective UAE study ever to be performed (Pron *et al*: 555 Canadian women undergoing UAE at eight Ontario university and community

hospitals) (42). Our cohort (54% Caucasian, 40% African American, 6% Asian) had an average age of 45, similar to the Pron *et al* cohort (66% Caucasian, 23% black, 11% Asian) which had a average age of 43. The only respect in which our cohort was considerably different at baseline was with respect to pre-UAE uterine and largest fibroid volumes: our cohort had a larger pre-UAE mean total uterine volume (842 cc, versus 704 cc in the Pron *et al* cohort) and a larger pre-UAE mean largest fibroid volume (348 cc, versus 308 cc in the Pron *et al* cohort).

In terms of women's primary reason for seeking treatment, we found that the most common reasons were bleeding (53%), pain (51%), bulk symptoms (31%), urinary symptoms (22%), bowel symptoms (4%), and dyspareunia (4%). This information on self-reported reasons for seeking treatment is interesting in conjunction with our findings about sexual function: while only 4% of our cohort self-reported pain with sexual activity, when prompted with multiple-choice questions, the same cohort was found to have worse sexual function on every single scale of the FSFI -- including pain -- than healthy controls. A number of possibilities may explain this discrepancy, including: that women are not seeking interventional treatment for fibroids because of sexual dysfunction; that women do not think of fibroids as a possible cause of their sexual dysfunction; that women are not bothered by their sexual dysfunction; or, that women *are* bothered by their sexual dysfunction but are not raising the issue with their physicians. Thus, one practical benefit of our study is that it provides evidence in support of physicians asking women with fibroids about their sexual health.

In terms of frequency and percent of symptoms, we found that 81% of women reported urinary symptoms at least one-fourth of the days or more in the month prior to

the survey. This is similar to the Pron *et al* UFE trial in which 73% of patients reported urinary urgency/frequency at baseline (42). With respect to bleeding, 37% of our cohort reported bleeding symptoms at least one fourth of the days or more in the month prior to survey. This is also similar to the Pron *et al* UFE trial, in which 31% of the women reported lengthy, i.e., longer than seven days, menstrual periods.

In terms of quality of life, we found that women seeking UAE for symptomatic fibroids reported minimally to moderately worse health-related quality of life with respect to physical role, bodily pain, vitality, and social functioning on the SF-36 than the general female population. These findings extend the work by Spies *et al*, who adapted the SF-36 for women with uterine fibroids, but found small-to-moderate correlations between his fibroid-specific HRQOL measure and the SF-36 when validating his instrument (12). Our confirmation utilizing the SF-36, a widely used measure of health related quality of life, that women seeking UAE for symptomatic fibroids had worse health-related quality of life than healthy women is striking given the prevalence of the condition in women of reproductive age. We did, however, find that our cohort of women with fibroids had *better* quality of life with respect to general health than the general female population, which may reflect the fact that our cohort with fibroids was largely healthy women without other comorbidities.

In terms of sexual function, we found that women seeking UAE for symptomatic fibroids reported worse sexual function in all areas -- including desire, arousal, lubrication, orgasm, satisfaction and pain -- and on the full scale score than healthy women controls. This is consistent with a recent population-based cross-sectional study by Lippman *et al* who found that women with fibroids were more likely to report

moderate or severe dyspareunia than women without fibroids (43). Spies *et al* also reported that women with fibroids had worse sexual function than normal controls, but this conclusion was drawn from answers to a limited number (two) of questions (“During the previous three months, how often have your symptoms related to uterine fibroids diminished your sexual desire? Caused you to avoid sexual relations?”) (12). Thus, our confirmation with the FSFI, an empirically validated 19-item measure of female sexual function, that women with symptomatic fibroids have worse sexual function than healthy women controls both replicates and extends the work of Spies *et al*.

We found that urinary symptoms were related to larger uterine and fibroid size. This is particularly relevant given that the present study also found that 81% of women reported urinary symptoms at least one fourth of the days or more in the month prior to survey. This is an important finding that needs to be followed up with treatment-outcome research to examine whether decrease in uterine and fibroid size post-UAE decreases urinary as well as other fibroid-related symptoms as well, something our post-UAE data only preliminarily begins to investigate. However, in terms of pretreatment data, to our knowledge, no published studies exist examining the correlation between baseline uterine and fibroid size, and fibroid-related symptoms other than bleeding, including quality of life and sexual function.

In terms of quality of life, we found that three aspects of quality of life – including physical function, general health, and bodily pain – were significantly correlated with either total uterine volume or largest fibroid volume. The fact that the bodily pain scale of the SF-36 was significantly correlated with largest fibroid volume is consonant with our finding that pain as a fibroid-related symptoms was significantly

correlated with total uterine volume, given that total uterine volume is a function of largest fibroid volume plus volume contributed by other fibroids, if present. These findings suggest that pain is in some way related to larger volume, potentially because of compression from mass effect. The fact that physical function and general health were also correlated with total uterine volume implies that beyond individual symptoms, fibroids may impact to some degree on overall quality of life depending on the size of the uterus. However, the majority of quality of life subscales were not correlated with total uterine volume or largest fibroid volume. These results are consistent with Pron *et al*, who asked women to rate the overall impact or interference of fibroids on their daily lives on a scale from one (little or minimal interference) to ten (total or complete interference with their daily or usual activities), and found that uterine and fibroid size were not responsible for high “life impact” scores in some cohorts (42).

No aspects of sexual function, including pain, were significantly correlated with either MRI-determined total uterine volume or largest fibroid volume, despite the fact that our cohort of women with fibroids was found to have worse sexual function on every FSFI scale than healthy women controls. Lippman *et al* also reported that total volume of fibroids was not related to dyspareunia using different assessment methods (i.e., ultrasound-generated volume data and a visual analog scale) (43). Thus, our confirmation with MRI and the validated FSFI that pain with respect to sexual function is not correlated with volume in women with symptomatic fibroids seeking UAE both replicates and extends the work of Lippman *et al*, who studied a non-care-seeking population. This emphasizes that physicians should routinely asking women with fibroids about their sexual function, irrespective of uterine or largest fibroid size. More research is

needed to better understand what may account for differences in sexual function between women with fibroids and women without fibroids (e.g., fibroid neovascularization).

With respect to fibroid location, our results are consonant with the literature: for example, our rate of submucosal fibroids (30%) was similar to that found by Kjerulff *et al* (27% overall) in their pathological analysis of hysterectomy specimens (44). In terms of the potential relationship between fibroid location and symptoms, our results do not support the contention of some that fibroids located submucosally contribute disproportionately to heavy bleeding than fibroids in other locations (7). In contrast, we found that the presence of submucosal fibroids did not appear to have a significant effect on any fibroid-related symptoms, including bleeding. This is consistent with recent work by Wegienka *et al* who found that nonsubmucosal fibroids were associated with heavy bleeding to the same extent as submucosal fibroids (6). Our results also do not support the literature that subserosal fibroids contribute disproportionately to pressure and pain. In contrast, we found that the presence of subserosal fibroids did not appear to have a significant effect on any fibroid-related symptoms, including pain. Although our analysis was limited by small sample size, and non-equal groups potentially confounded by the presence of fibroids in other locations, our findings suggest that in contrast to endometriosis in which the anatomic location of endometriosis *does* effect pelvic pain symptoms (9), the anatomic location of fibroids – specifically those located subserosally or submucosally -- does not appear to be related to fibroid-related symptoms.

Our study of the impact of MRI-determined uterine and fibroid size and fibroid position on fibroid-related symptoms, including quality of life and sexual function, adds a new dimension to the existing body of literature: although abdominal and transvaginal

ultrasound have been used in attempting to characterize the relationship between bleeding symptoms and fibroid size and location (6), we are unaware of any published studies that utilize MRI to measure the size and location of fibroids while investigating such relationships. Dueholm *et al* found that the mean number of correctly identified myomas was significantly higher by magnetic resonance imaging than by transvaginal ultrasound (45).

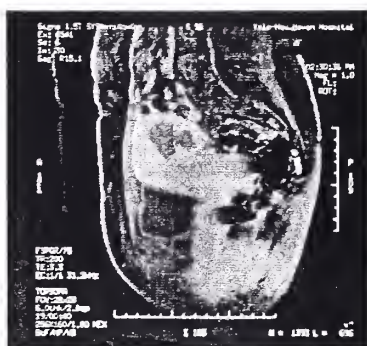
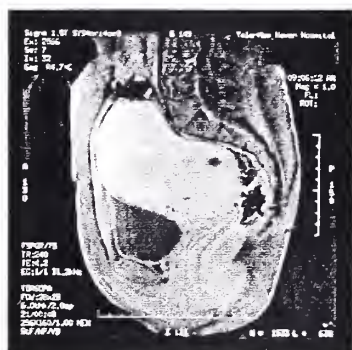
Post-UAE Data

The third hypothesis of this research was that uterine and fibroid size would significantly decrease after treatment with UAE, and that fibroid-related symptoms would improve. However, the small sample size at follow-up post-UAE (37/52=71% for questionnaires, 17/46=37% for MRIs) and the possibility of reporting bias among these patients limits the reliability of conclusions generated from the data. Results in this arm of the research must be considered as preliminary/pilot data only, guiding future research.

While uterine and largest fibroid volume reductions were 35% and 42% respectively three months after UAE in the Pron *et al* UFE Trial (46) and 34% and 50% respectively 4.4 months after UAE in a trial by Spies *et al* (48), we found a 41% reduction in uterine volume and 35% reduction in largest fibroid volume from pre- to post-UAE (Figure 2). Thus, despite the limitations of our data, our volume reductions were consistent with the literature.

Figure 2. Sagittal MRI of a fibroid uterus a) pre-UAE, and b) six months post-UAE.

a) b)



In terms of symptom relief, our preliminary data revealed that the most substantial improvements were in urinary and pain symptoms, with the frequency of both nearly halving from baseline to follow-up: 81% of patients pre-UAE versus 49% of patients post-UAE reported urinary frequency/urgency at least one fourth of days per month; 81% of patients pre-UAE versus 46% of patients post-UAE reported pain at least one fourth of days per month). It would be important for future research to focus on investigating whether change in uterine and fibroid volume correlates with changes in fibroid-related symptoms. This is of particular interest given findings by de Souza *et al* that volume reduction did not correlate with improvement in fibroid-related symptoms (47), by Pron *et al* that improvements in menorrhagia were unrelated to post-UAE volume reduction (46), and by Spies *et al* that the odds of improved bulk-related symptoms were not associated with fibroid-volume change (48).

Post UAE, we found that quality of life scores improved in all SF-36 scales, with a statistically significant improvement in the subscales of physical function and bodily pain. Although only preliminary data, significant improvements in these two areas is

important, given that both were correlated with volume measurements pretreatment (i.e., physical function correlated with total uterine volume, $p=.04$; bodily pain correlated with largest fibroid volume, $p=.02$). This begs the question of whether post-treatment improvement in symptoms, including quality of life, correlate with post-treatment improvement (i.e., decrease) in uterine and fibroid size, although recent results from de Souza *et al*, Pron *et al*, and Spies *et al* detailed above suggest that this may not be the case.

Preliminary results with respect to post-UAE quality of life were consistent with the limited literature in this area: Spies *et al* also found that health-related quality of life scores improved at all instances at follow-up post-UAE (48). Our confirmation with the SF-36, a widely used measure of health related quality of life, that women reported improved health-related quality of life after UAE both replicates and extends the work of Spies *et al*, albeit with a smaller sample size. Our findings in this area are also important given mixed reports in the literature about quality of life after hysterectomy, although few (six total, two relevant, based on a PubMed search of “hysterectomy” and “SF-36”) utilize the SF-36 as we do. While Lambden *et al* report that women undergoing hysterectomy for nononcologic reasons had improved health status and psychological well-being as measured by the SF-36 in the initial period after surgery (49), in contrast, Byles *et al* reported that women who had had hysterectomy had significantly poorer physical and mental health as measured by the SF-36 quality of life profile than women who had not had hysterectomy (50).

Post UAE, we found no significant change in sexual function in comparison with pretreatment. On the one hand, it may be disappointing that there was not an

improvement in sexual function given our finding that women with fibroids have significantly worse sexual function than normal controls. On the other hand, the results are encouraging in light of previous case reports about sexual dysfunction after UAE (35). It is also important given recent reports in the literature about sexual dysfunction after hysterectomy. Roovers *et al* reported that the prevalence of one or more bothersome sexual problems after vaginal hysterectomy, subtotal abdominal hysterectomy, and total abdominal hysterectomy was 43%, 41% and 39%, respectively (51). Additionally, in another study comparing total laparoscopic hysterectomy and laparoscopically assisted vaginal hysterectomy, Long *et al* found a significant reduction in the frequency of orgasms after surgery in both groups ($p < .05$) (52). These newer studies stand in contrast to previous reports by Weber *et al*, who reported no change in sexual functioning after abdominal hysterectomy (53), and by Rhodes *et al*, who reported that sexual functioning improved overall after hysterectomy, with the frequency of sexual activity increasing and problems with sexual functioning (e.g., dyspareunia, inorgasmia, low libido) decreasing (54).

Exactly how hysterectomy could cause sexual dysfunction is not clear; both abstract and anatomically-based theories have been proposed. First, as Roovers *et al* write, “historically the uterus has been regarded as the regulator and controller of important physiological functions, a sexual organ, a source of energy and vitality, and a maintainer of youth and attractiveness. Women are concerned that hysterectomy may affect their sexual wellbeing or their sexual attractiveness” (51). Second, the pelvic autonomic nerve plexus may be damaged during hysterectomy in several ways: during division of the cardinal ligaments, the main branches of the nerve plexus that pass under



the uterine arteries may be damaged; cervical removal may result in the loss of a large part of the nerve plexus; or if a radical hysterectomy is being performed, the major part of the vesical innervation may be damaged during blunt dissection of the bladder from the uterus and cervix (56, 57). In contrast, UAE avoids the surgical disruption of pelvic nerve plexi intimately involved in female sexual response and pleasure.

Changing trends in gynecologists' opinion of UAE

Overtime, we observed that a greater proportion of our UAE patients seemed to be referred by gynecologists, rather than self-referred, and therefore the fourth hypothesis of our research was that more gynecologists had a favorable opinion of UAE and were offering UAE in comparison to two years earlier. Our telephone survey confirmed this hypothesis, revealing a trend of increasing acceptance by gynecologists of UAE for fibroids, as perceived by their patients. This research extends the literature in this area by providing an examination of gynecologists' changing opinion of UAE over time, albeit an indirect one. Since UAE is a relatively new treatment for uterine fibroids, and since gynecologists are most often the primary physicians who counsel patients about treatment options, their knowledge, attitude and acceptance of UAE as a treatment modality is of critical importance.

Based on patients' reports of their gynecologists, the following specific trends were noted: fewer gynecologists appeared to be initially opposed to UAE in the second survey (33%) than in the first (76%); a greater number of gynecologists offered UAE as a treatment option in the second survey (38%) than in the first (5%); and a greater number of gynecologists initiated discussion of UAE with their patients in the second survey



(43%) than in the first (10%). However, despite these significant gains, according to patients' reports, 62% of gynecologists still did not offer UAE as a treatment option for fibroids. This is disconcerting, since informed consent dictates discussion of all treatment options available.

Although there appears to be an overall increasing acceptance of UAE by gynecologists, there was no significant difference in the percentage of patients who did not return to gynecologists perceived by their patients to be initially opposed to UAE when comparing the first and second surveys. It may well be that gynecologists who fail to discuss UAE or communicate a negative attitude towards the procedure may risk losing their patients.

Seventy-one percent of women in the second survey group had Internet access at home, and 62% used the Internet to learn about UAE. Thus, if gynecologists do not discuss UAE as a treatment option, it appears that many patients will learn about the procedure through the Internet themselves. Physician-conveyed information would promote a healthier doctor-patient relationship, as well as counter misinformation contained within unregulated Internet sites.

Limitations

There are several limitations to our research. First, the study was limited to women with fibroids who were symptomatic and seeking interventional treatment. Therefore, our results do not necessarily apply to women with fibroids who are asymptomatic or symptomatic but seeking non-interventional treatment (i.e., medical treatment, myomectomy, hysterectomy). Second, our SF-36 quality of life and FSFI

sexual function analyses used historical controls collected by other investigators, and therefore were unable to control for potential confounders such as the presence of fibroids in women in the control groups. Third, the fact that patients could have had other health issues that potentially could have caused pain or urinary symptoms (e.g., chronic interstitial cystitis), pressure (e.g., benign ovarian cyst), or bowel symptoms (e.g., inflammatory bowel disease), was not controlled for in our analyses. Fourth, we note the possibility of reporting bias: some of the patients who underwent UAE left items blank on the questionnaire or did not answer the questionnaire at all at follow-up; they might have experienced detrimental effects which were not included in analyses. Furthermore, a large number of women who completed follow-up questionnaires had not yet reached the time, or failed to return, for the six month post-UAE MRI and therefore were also not included in analyses. Fifth, our follow-up questionnaire data was accrued between one and six months after UAE, instead of at one specific time point. Sixth, we note our small sample size.

In terms of the telephone survey, there were several limitations as well. First, the study was limited to women's perceptions of their gynecologists' opinion of UAE. Therefore, while patients' perceptions of gynecologists' opinion of the procedure are important in that they may impact whether a patient stays with the same gynecologist, the results of this study do not necessarily reflect gynecologists' actual opinion of the procedure. Second, the study was limited to surveying women undergoing UAE at one specific practice site, and therefore may reflect locally but not necessarily nationally changing trends in gynecologists' opinion of UAE.

CONCLUSIONS

In summary, in this largely prospective multi-disciplinary study, we examined radiological, physiological and psychosocial variables in premenopausal women with symptomatic uterine fibroids before and after uterine artery embolization.

We hypothesized about the relationship between baseline uterine and fibroid size and fibroid position, and baseline fibroid-related symptoms. We found that MRI-determined uterine and largest fibroid size, but not fibroid position, appear to effect urinary symptoms and some aspects of quality of life, but not sexual function. We also hypothesized that women with symptomatic uterine fibroids have impaired quality of life and sexual function. In addition to urinary, pain, bleeding and bowel symptoms, we found that women with symptomatic fibroids had worse quality of life and sexual function than healthy controls. Based on these findings, it is recommended that health care providers treating women with uterine fibroids specifically ask about quality of life and sexual function, because women may be unaware of their impaired function or may not raise the issue themselves.

Post-UAE, we hypothesized that there would be a decrease in uterine and fibroid size, and an improvement in fibroid-related symptoms. We found that uterine and fibroid volume decreased significantly, and that there were significant improvements in urinary and pain symptoms, as well as some aspects of quality of life. Future research tracking fibroid-related symptoms, including quality of life and sexual function should be performed in a consistent manner before and after a variety of treatment modalities, in order to establish evidence-based treatment guidelines.

In view of our telephone survey results that more gynecologists had a favorable opinion of UAE and were offering UAE currently in comparison to two years previously, it is recommended that Interventional Radiologists treating women with UAE continue to work actively to create a positive relationship with gynecologists, involving the referring MD before, during and after the UAE procedure, in order to enhance the acceptance of this safe, effective procedure.

In conclusion, our research illustrates that women with symptomatic leiomyomata seeking UAE are burdened with troublesome fibroid-related symptoms and impaired quality of life and sexual function. UAE, increasingly accepted by gynecologists, reduces uterine and fibroid volume and provides improvement in fibroid-related symptoms, including some aspects of quality of life, without worsening sexual function. Continued multidisciplinary research such as this involving radiologists, gynecologists and psychologists has the potential to greatly assist physicians and patients alike to make more informed decisions about the treatment of this highly prevalent women's health condition.

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Appendix A: Peer-Reviewed Articles

Arleo, E.K., Masheb, R.M., and Tal, M.G. 2004. Uterine Fibroids and Sexual Dysfunction: True, True and Related? *Female Patient*. In press.

Arleo, E.K., and Tal, M.G. 2004. Uterine Fibroids: Medical, Surgical, and Interventional Radiology Treatment Options. *Female Patient*. In press.

Arleo, E.K., Pollak, J., and Tal, M.G. 2003. Changing Trends in Gynecologists' Opinions of Uterine Artery Embolization for Fibroids: The Patient's Perspective. *J Vasc Interv Radiol*. 14:1559-1561.

Arleo, E.K., Pollak, J., and Tal, M.G. 2003. Changing Trends in Gynecologists' Opinions of Uterine Artery Embolization for Fibroids: The Patient's Perspective. *J Vasc Interv Radiol*. 14:1559-1561.

Changing Trends in Gynecologists' Opinions of Uterine Artery Embolization for Fibroids: The Patient's Perspective

Elizabeth Kagan Arleo, BA, Jeffrey Pollak, MD, and Michael G. Tal, MD

This study's purpose was to survey patients' perceptions of gynecologists' opinions of uterine artery embolization (UAE) for fibroids. Twenty-one women who underwent UAE between July 2000 and April 2002 and 21 women who underwent UAE between September 1998 and July 2000 completed questionnaires. Each woman was asked what her gynecologist's initial opinion was toward UAE, what treatment options were offered, who initiated discussion of UAE, and whether she returned to the same gynecologist after UAE. As of 2002, more gynecologists had a favorable opinion of UAE and were offering UAE versus in the year 2000. The majority of patients whose gynecologists initially opposed UAE did not return to the same gynecologists, reflecting a similar trend noted 2 years earlier.

J Vasc Interv Radiol 2003; 14:1559-1561

Abbreviation: UAE = uterine artery embolization

GIVEN that gynecologists have traditionally been the providers of treatment for uterine fibroids, the purpose of this article is to investigate gynecologists' opinion of uterine artery embolization (UAE), a relatively new treatment option provided by interventional radiologists. Uterine fibroids, also known as leiomyomata, affect 30%-40% of women of reproductive age in the United States (1). Fibroids are symptomatic in 35%-50% of women who have them, causing menorrhagia, pressure-related symptoms (bloating, urinary frequency or retention, constipation), pain (dysmenorrhea, dyspareunia), and reproductive difficulties (infertility, miscarriage). Medical treatment options for symptomatic fibroids include gonado-

tropin-releasing hormone analogues (2) and, more recently, danazol and gestrinone (3), whereas surgical treatment options include hysterectomy and myomectomy. More recently, UAE, a minimally invasive alternative therapy performed by interventional radiologists, has been used as a primary treatment for symptomatic uterine fibroids. Hysterectomy is currently the most common surgical treatment for women with uterine fibroids, and fibroids are the number-one indication for performing hysterectomy: 40% of the estimated 600,000 hysterectomies performed annually in the United States are performed for fibroids (4).

UAE for fibroids, first described by Ravina et al in 1995 (5), has been gaining popularity for several reasons: the procedure is minimally invasive with little blood loss, is associated with less morbidity, requires shorter hospitalization during recovery, and allows for preservation of the uterus (6-13). However, the American College of Obstetricians and Gynecologists Practice Bulletin, which provides clinical management guidelines for obstetricians and gynecologists, states that "uterine artery embolization is regarded as investigational" (14). However, anecdotal evidence suggests that

gynecologists' opinions may be changing over time as more women seek uterine-preserving treatments for symptomatic fibroids.

Given the prevalence of fibroids, the increasing role of UAE in treating them, and the lack of data examining gynecologists' opinion of the procedure, the aims of the present study were to survey patients' perceptions of their gynecologists' expressed opinions of UAE and to compare these results to those of the same survey conducted 2 years earlier.

MATERIALS AND METHODS

In August 1998, a telephone study was initiated to assess patients' perspective of their gynecologists' opinion of UAE and to examine changing trends, if any. The surveys were administered during two time frames: from August 1998 to July 2000 and from July 2000 to April 2002. Twenty-one patients completed the survey during each time frame.

For entry into the study, patients were required to have undergone UAE for symptomatic uterine fibroids at the practice site and be participating in another survey regarding UAE conducted by the same principal investi-

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Telephone Survey Results

	Time Period		P Value
	August 1998 to July 2000	July 2000 to April 2002	
No. of respondents	21/50 (42)	21/39 (54)	
Gynecologists initially opposed or strongly opposed to UAE	16/21 (76)	7/21 (33)	<.05
Gynecologists who offered UAE as a treatment option	1/21 (5)	8/21 (38)	<.05
Gynecologists who initiated discussion of UAE with their patients	2/21 (10)	9/21 (43)	<.05
Patients who did not return to gynecologists who were initially opposed to UAE	8/9 (89)	5/7 (71)	NS

Note.—Values in parentheses are percentages.

gators. Patients were self-referred or referred by gynecologists for treatment. Exclusion criteria were malignancy and postmenopausal status.

Each participant was asked to rate her gynecologist's initial opinion of UAE before the procedure on a scale from 1 (strongly opposed) to 6 (very favorable) or 7 (unaware of the procedure); whether the gynecologist offered UAE as a treatment option; whether she or the gynecologist initiated discussion of UAE; and whether she continued to see the same gynecologist after the procedure. In the second survey, each participant was also asked whether she had Internet access at home and whether she used the Internet to learn about UAE.

Data were analyzed with use of Statcalc 1.1 (StatCalc Software, Etext.net publisher, Venice, CA). Frequency and percentiles were calculated for categoric variables. All reported *P* values were based on Fisher exact tests. The study was reviewed and approved by the hospital's human investigation committee.

RESULTS

The two survey groups were quite similar. The mean patient ages were 45.4 years in the first survey and 44.2 years in the second. Seventy-five percent of respondents to the first survey and 73% of respondents to the second survey had earned at least a 4-year college degree (differences not statistically significant, Fisher exact test, *P* > .05).

The Table contains the results of the telephone surveys during both time frames. There was a significant difference in the number of gynecologists initially opposed to UAE (*P* < .05), with fewer gynecologists initially opposed to UAE in the second survey in comparison with the first. There was also a significant difference in the number of gynecologists who offered UAE as a treatment option (*P* < .05), with more gynecologists offering UAE as a treatment option in the second survey in comparison with the first. In addition, there was a significant difference in the number of gynecologists who initiated discussion of UAE with their patients (*P* < .05), with more gynecologists initiating discussion of UAE with their patients in the second survey in comparison with the first. Finally, there was no significant difference in the percentage of patients who did not return to gynecologists who were initially opposed to UAE when comparing the two surveys.

Participants in the second survey were also queried regarding whether they had the Internet at home and whether they used the Internet to learn about UAE. Seventy-one percent (15 of 21) reported they had Internet access at home, and 62% (13 of 21) reported that they used the Internet to learn about UAE.

DISCUSSION

This study revealed a trend of increasing acceptance by gynecologists of UAE for treatment of symptomatic

uterine fibroids. This research extends the literature in this area by providing an examination of gynecologists' changing opinions of UAE over time. Because UAE is a relatively new treatment for uterine fibroids, and because gynecologists are most often the primary physicians who counsel patients about treatment options, their knowledge, attitude, and acceptance of UAE as a treatment modality is of critical importance.

With regard to specific trends, it was found that fewer gynecologists were initially opposed to UAE in the second survey (33%) than in the first (76%). In addition, there was a greater number of gynecologists offering UAE as a treatment option in the second survey (38%) than in the first (5%), and a greater number of gynecologists initiated discussion of UAE with their patients in the second survey time frame (43%) than in the first (10%). Despite these significant gains, 62% of gynecologists still do not offer UAE as a treatment option for fibroids. This is disconcerting because informed consent dictates discussion of all treatment options.

Although there appears to be an overall increasing acceptance of UAE by gynecologists, there was no significant difference in the percentage of patients who did not return to gynecologists initially opposed to UAE when comparing the first (50%) and second (71%) surveys. It may well be that gynecologists who fail to discuss UAE or communicate a negative attitude toward the procedure may risk losing their patients.

Seventy-one percent of participants had Internet access at home, and 62% of participants used the Internet to learn about UAE. Therefore, if gynecologists do not discuss UAE as a treatment option, it appears that many patients will learn about the procedure through the Internet anyway. Up-front physician-conveyed information would promote a healthier doctor-patient relationship as well as counter misinformation sometimes present on unregulated Internet sites.

There are several limitations to this study. First, the study was limited to women's perceptions of their gynecologists' opinions of UAE. Therefore, although patients' perceptions of gynecologists' opinions of the procedure are important in that they may impact

whether patients stay with the same gynecologists, the results of this study do not necessarily reflect gynecologists' actual opinions of the procedure. Second, because the study was limited to women with fibroids that were symptomatic to the extent that interventional treatment was sought, the results of this study do not necessarily apply to the gynecologists of women with fibroids that were asymptomatic or symptomatic but did not prompt operative treatment. The treatment options and opinions offered by these gynecologists may have been different. Third, the study was limited to surveys of women undergoing UAE at one specific practice site and therefore may reflect locally but not necessarily nationally changing trends in gynecologists' opinions of UAE.

In conclusion, a trend of increasing acceptance by gynecologists of UAE for treatment of symptomatic uterine fibroids was found. It is recommended that interventional radiologists treating women with UAE work actively to create positive relationships with gynecologists and make an effort to get them involved before, during, and after the UAE procedure. In this way, the trend of greater acceptance of this safe, effective procedure for the treat-

ment of this highly prevalent women's health condition will be enhanced.

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Appendix B: Published Abstracts

Arleo, E.K., Purushothaman, K., Masheb, R.M., and Tal, M.G. 2004. Correlation between increased blood flow to pelvic organs and improvement in urinary symptoms after UFE. *J Vasc Interv Radiol*. In press. (Abstr.)

Arleo, E.K., Masheb, R.M., Pollak, J., McCarthy S., and Tal, M.G. 2003. Relationship between Fibroid Location and Volume, and Fibroid-Related Symptoms: Do Position or Size Matter?" *Radiological Society of North America 89th Scientific Assembly and Annual Meeting Program*. 456. (Abstr.)

Arleo, E.K., Masheb, R.M., Pollak, J., and Tal, M.G. 2003. Relationship between Uterine and Fibroid Volume, and Fibroid-Related Symptoms and Sexual Functioning in Premenopausal Women with Leiomyomata. *AJR*. 180:23. (Abstr.)

Arleo, E.K., Masheb, R.M., and Tal, M.G. 2003. Quality of Life and Sexual Functioning in Premenopausal Women with Leiomyomata. *Obstet Gynecol*. 101:56S. (Abstr.)

Arleo, E.K., Masheb, R.M., Pollak, J., and Tal, M.G. 2003. Relationship between Uterine and Fibroid Volume, and Fibroid-Related Symptoms and Sexual Functioning in Premenopausal Women with Leiomyomata. *J Vasc Interv Radiol*. 14:S82. (Abstr.)

Arleo, E.K., Pollak, J., and Tal, M.G. 2003. Changing Trends in Gynecologists' Opinions of Uterine Fibroid Embolization (UFE). *J Vasc Interv Radiol*. 14:S81. (Abstr.)

Arleo, E.K., Masheb, R.M., Pollak, J., McCarthy S., and Tal, M.G. 2003. Relationship between Fibroid Location and Volume, and Fibroid-Related Symptoms: Do Position or Size Matter?" *Radiological Society of North America 89th Scientific Assembly and Annual Meeting Program*. 456. (Abstr.)

624 • 11:30 AM

Relationship between Fibroid Location and Volume, and Fibroid-Related Symptoms: Do Position or Size Matter?

(FBA)

E.K. Arleo, MD, New Haven, CT • R.M. Masheb, PhD • J.S. Pollak, MD • S.M. McCarthy, MD, PhD • M.G. Tal, MD (Michael.tal@yale.edu)

PURPOSE: To determine the relationship between MRI-determined fibroid location, largest fibroid volume (LFV) and total uterine volume (TUV), and fibroid-related symptoms in premenopausal women with symptomatic uterine fibroids.

METHOD AND MATERIALS: Eighty premenopausal women undergoing uterine fibroid embolization (UFE) received a pre-procedural pelvic MRI and self-report questionnaire investigating the frequency of fibroid-related symptoms, including pain, urinary, bowel, and bleeding symptoms. From MRIs, the presence of submucosal fibroids (SMF), intramural fibroids with a submucosal component (IMFSC), intramural fibroids (IMF), subserosal fibroids with an intramural component (SSFIC), and subserosal fibroids (SSF) were noted, and LFV and TUV were calculated. The frequencies of fibroids in the different locations defined above and the frequencies of fibroid-related symptoms in the month prior to UFE were calculated. Statistical analyses were then performed to determine whether there were relationships between fibroid location, LFV and TUV, and fibroid-related symptoms.

RESULTS: Ninety-two percent of patients had IMF, 56% had SSF, 26% had IMFSC, 26% had SMF, and 5% had SSFIC. Pain was associated with the presence of IMFSC ($p=.013$). Pain, urinary, bowel, and bleeding symptoms were not significantly associated with the presence of fibroids in any other locations. LFV and TUV were significantly correlated with urinary symptoms ($p=.017$ and $p=.007$, respectively). There was no correlation between LFV or TUV and pain, bowel, and bleeding symptoms.

CONCLUSIONS: In premenopausal women with symptomatic uterine fibroids, there was a significant relationship between fibroids located intramurally with a submucosal component and pain symptoms, as well as between fibroid and uterine volume, and urinary symptoms. No other significant relationships were found.

Arleo, E.K., Masheb, R.M., Pollak, J., and Tal, M.G. 2003. Relationship between Uterine and Fibroid Volume, and Fibroid-Related Symptoms and Sexual Functioning in Premenopausal Women with Leiomyomata. *AJR*. 180:23. (Abstr.)

3:20 PM

092. Relationship between Uterine and Fibroid Volume and Fibroid-Related Symptoms and Sexual Functioning in Premenopausal Women with Leiomyomata

Arleo E.K.^{1*}; Masheb R.²; Tal M.G.¹ 1. *Department of Radiology, Yale University, New Haven, CT*; 2. *Department of Psychiatry, Yale University, New Haven, CT*

Objectives: To determine the relationship between uterine and fibroid volume, and fibroid-related symptoms and sexual functioning in premenopausal women with leiomyomata.

Methods: Women undergoing UFE for leiomyomata received a pre-operative MRI and self-report questionnaires. Total uterine volume (TUV) and largest fibroid volume were obtained from pre-operative MRIs. Participants completed a questionnaire of fibroid-related symptoms including pelvic pain, urinary and bowel symptoms, and bleeding. In addition, participants completed the Female Sexual Functioning Index (FSFI), an empirically validated measure including subscales for sexual desire, arousal, lubrication, orgasm, satisfaction, and dyspareunia. The frequencies of fibroid-related symptoms in the month prior to UFE, and mean scores for each subscale of the FSFI, were calculated. Relationships between the two volumes, and the fibroid-related symptoms and FSFI subscales were examined using Pearson correlation coefficients.

Results: Thirty women with confirmed leiomyomata received pre-operative MRIs and completed the questionnaires. TUV was moderately correlated with urinary symptoms ($r=.40$) and several aspects of sexual functioning, including sexual desire, orgasm and dyspareunia ($r=.47$, $.48$ and $.50$, respectively) at least at the $.05$ level. However, the volume of the largest fibroid did not correlate significantly with either fibroid-related symptoms or sexual functioning.

Conclusions: TUV, but not fibroid volume, was related to urinary symptoms and aspects of sexual functioning in premenopausal women with leiomyomata.

Arleo, E.K., Masheb, R.M., and Tal, M.G. 2003. Quality of Life and Sexual Functioning in Premenopausal Women with Leiomyomata. *Obstet Gynecol.* 101:56S. (Abstr.)

Quality of Life and Sexual Functioning in Premenopausal Women With Leiomyomata

Elizabeth Kagan Arleo

Yale University School of Medicine, New Haven, CT

Robin M. Masheb, PhD, and Michael Tal, MD

OBJECTIVE: To characterize quality of life and sexual functioning in premenopausal women with leiomyomata.

METHODS: Women undergoing uterine fibroid embolization (UFE) for leiomyomata received a preoperative MRI and health-related quality of life and sexual functioning questionnaire. The questionnaire contained empirically validated measures, including the Short Form 36 (SF-36) and the Female Sexual Functioning Index (FSFI). Mean scores for each subscale of the SF-36 and FSFI were calculated and effect sizes were computed, using norms for healthy and patient populations. In addition, correlations with total intrauterine volume (TIUV), obtained from preoperative MRIs, and subscales from the FSFI were computed.

RESULTS: Forty women with confirmed leiomyomata completed the questionnaire. Differences in quality of life scores between women with leiomyomata and the US female population were small. However, differences in sexual functioning scores between women with leiomyomata and healthy women were significant on all subscales, at least at the .05 level, with effect sizes ranging from medium to large (-0.42 to -1.16). Furthermore, women with leiomyomata did not significantly differ from women with female sexual arousal disorder with respect to dyspareunia. Among women with leiomyomata, several aspects of sexual functioning were significantly related to TIUV, including desire, orgasm, and dyspareunia ($P = .026$, $.021$, and $.019$, respectively).

CONCLUSIONS: Participants with leiomyomata had health-related quality of life comparable to that of the general population. However, their sexual functioning was below that of healthy women, especially with regard to dyspareunia.

Arleo, E.K., Masheb, R.M., Pollak, J., and Tal, M.G. 2003. Relationship between Uterine and Fibroid Volume, and Fibroid-Related Symptoms and Sexual Functioning in Premenopausal Women with Leiomyomata. *J Vasc Interv Radiol.* 14:S82. (Abstr.)

4:44 PM

Abstract No. 238

Relationship between Uterine and Fibroid Volume, and Fibroid-Related Symptoms and Sexual Functioning in PreMenopausal Women with Leiomyomata.

E.K. Arleo, Yale University, New Haven, CT, USA • R.

Masheb • J. Pollak • M.G. Tal

PURPOSE: To determine the relationship between uterine and fibroid volume, and fibroid-related symptoms and sexual functioning in premenopausal women with leiomyomata.

MATERIALS AND METHODS: Women undergoing UFE for leiomyomata received a pre-operative MRI and self-report questionnaires. Total uterine volume (TUV) and largest fibroid volume were obtained from pre-operative MRIs. Participants completed a questionnaire of fibroid-related symptoms including pelvic pain, urinary and bowel symptoms, non-menstrual bleeding and hot flashes. In addition, participants completed the Female Sexual Functioning Index (FSFI), an empirically validated measure including subscales for sexual desire, arousal, lubrication, orgasm, satisfaction, and dyspareunia. The frequencies of fibroid-related symptoms in the month prior to UFE, and mean scores for each subscale of the FSFI, were calculated. Correlations between the two volumes, and the fibroid-related symptoms and FSFI subscales were then computed.

RESULTS: Thirty women with confirmed leiomyomata received pre-operative MRIs and completed the questionnaires. TUV was significantly correlated with urinary symptoms ($p=.038$) and several aspects of sexual functioning, including sexual desire, orgasm and dyspareunia ($p=.026$, $.021$ and $.019$, respectively). However, the volume of the largest fibroid was not significantly correlated with either fibroid-related symptoms or sexual functioning.

CONCLUSION: TUV, but not fibroid volume, was related to urinary symptoms and aspects of sexual functioning in premenopausal women with leiomyomata.

Arleo, E.K., Pollak, J., and Tal, M.G. 2003. Changing Trends in Gynecologists' Opinions of Uterine Fibroid Embolization (UFE). *J Vasc Interv Radiol.* 14:S81. (Abstr.)

Scientific Session 29

UFE: Clinical Practice

Monday, March, 31, 2003

4:00 PM - 6:00 PM

Moderator(s): Anne C. Roberts, MD

Robert Worthington-Kirsch, MD

4:00 PM

Abstract No. 234

Changing Trends in Gynecologists Opinion of Uterine Fibroid Embolization (UFE).

E.K. Arleo, Yale University, New Haven, CT, USA • M.G.

Tal

PURPOSE: To evaluate the current opinion of gynecologists towards UFE, as perceived by patients, and compare it to the opinion of gynecologists towards UFE two years ago.

MATERIALS AND METHODS: Twenty-one women that underwent UFE between 7/00 to 4/02, completed a telephone survey thus far. They were asked what their gynecologists opinions were towards UFE, both before and after the procedure. In addition, they were asked if they see the same gynecologists that they saw before the procedure, what treatment options were offered to them and whether they or their gynecologist initiated discussion of UFE. These data were then compared to data obtained previously from 21 women that underwent UFE between 8/98 to 7/00.

RESULTS: Thirty-three percent (7/21) of gynecologists initially opposed or strongly opposed UFE, in contrast to 76% (16/21) of gynecologists from two years ago, this difference is statistically significant ($p < 0.05$). Seventy-one percent (5/7) of the patients did not return to the gynecologists that were initially opposed to the procedure and are now seeing other gynecologists. This is similar to data from two years ago, where 89% (8/9) of the patients did not return to the gynecologists that remained opposed to the procedure. While all gynecologists offered hysterectomy, just as they did two years ago, 38% (8/21) also offered UFE, in contrast to only 5% (1/21) of gynecologists two years ago, the difference is statistically significant ($p < 0.05$). Forty-three percent (9/21) of physicians initiated the discussion of UFE with their patients, a statistically significant increase from two years ago, when only 10% (2/21) of the physicians initiated discussion with their patients ($p < 0.05$).

CONCLUSION: More gynecologists are offering UFE as a treatment option for uterine fibroids and more have a favorable opinion towards UFE than two years ago. The majority of patients who underwent UFE whose gynecologist opposed the procedure did not continue seeing the same gynecologist, reflecting a similar trend as two years ago.

Appendix C: Presentations

Arleo E.K., Purushothaman, K., Masheb, R.M., and Tal, M.G. “Correlation Between Increased Blood Flow to Pelvic Organs and Improvement in Urinary Symptoms After UFE.” Society of Interventional Radiology, Phoenix, 25 March 2004. (Oral)

Arleo, E.K., Masheb, R.M., Pollak, J., McCarthy, S., and Tal, M.G. “Relationship between Fibroid Location and Volume, and Fibroid-Related Symptoms: Do Position or Size Matter?” Radiological Society of North America, Chicago, 2 December 2003. (Oral)

Arleo, E.K., Masheb, R.M., and Tal, M.G. “Relationship between Uterine and Fibroid Volume, and Fibroid-Related Symptoms and Sexual Functioning in Premenopausal Women with Leiomyomata.” Society of Interventional Radiology, Salt Lake City, 31 March 2003; American Roentgen Ray Society, San Diego, 5 May 2003. (Oral)

Arleo, E.K., and Tal, M.G. “Changing Trends in Gynecologists’ Opinion of Uterine Fibroid Embolization.” Society of Interventional Radiology, Salt Lake City, 31 March 2003. (Oral)

Arleo, E.K., Masheb, R.M., and Tal, M.G. “Quality of Life and Sexual Functioning in Premenopausal Women with Leiomyomata.” American College of Obstetricians and Gynecologists, New Orleans, 29 April 2003; Student Research Day, Yale University School of Medicine, 6 May 2003. (Poster)

Appendix D: Press Releases

Barnes, D.B. 20 Jan 2004. UFE for Uterine Fibroids Gains Doctors' Approval. www.fibroids1.com.

22 Dec 2003. Highlights from December's Journal of Vascular and Interventional Radiology. www.newswise.com.

8 Dec 2003. BioSphere Medical Reports Study Published in Journal of Vascular and Interventional Radiology. www.corporate-ir.net.

Thompson, T.L. 13 June 2003. Interventional rads put faith in UFE marketing, research despite skepticism of ob/gyns. www.auntminnie.com.



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FIBROIDS1 NEWS: Feature Story

UFE for Uterine Fibroids Gains Doctors' Approval

January 20, 2004

By Diana Barnes Brown for Fibroids1

A recent study conducted by Dr. Michael Tal and Elizabeth Kagan Arleo of the Yale University School of Medicine's Department of Diagnostic Radiology presented some positive findings about the efficacy and rates of doctor approval of uterine fibroid embolization (UFE) for uterine fibroids.

UFE is a minimally invasive procedure that can usually be performed on an outpatient basis. The procedure involves the use of a catheter that is fed through the femoral artery to the uterine artery and then used to administer a solution that blocks blood flow to the fibroid. Because fibroids require a relatively large quantity of blood to grow and survive in the uterus, blockage of blood flow to fibroids results in their shrinkage and the disappearance of symptoms for most patients, without requiring further treatment or the use of more invasive methods, such as hysterectomy.

The study, published in the December, 2003 issue of the Journal of Vascular and Interventional Radiology, showed that from 2000 to 2002, patients' perspectives about their gynecologists' opinions of UFE for fibroid tumors changed markedly. In a 2000 survey of 21 women, three quarters of those surveyed answered that they thought their gynecologists were opposed to UFE, while in a similar survey conducted in 2002, only a third of respondents answered that they thought their gynecologists were opposed to the use of UFE.

According to Dr. Tal, the jump in the treatment's popularity can be attributed to rising doctor and patient awareness, and also to innovations in embolization techniques and technologies, such as increased research and development of embolic agents, the solutions made up of tiny plastic particles that flow to targeted areas, blocking blood supply and thus shrinking fibroids. For this reason, he believes that doctors should discuss UFE with all patients who suffer from symptomatic uterine fibroids.

But, adds Ms. Arleo, over half of doctors are still reluctant to recommend UFE as a treatment option, a trend which she comments, is "disconcerting, especially since informed consent dictates discussion of all treatment options available."

The pair expressed hope that physicians will increasingly regard UFE as a viable and advantageous treatment option for patients.

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Source: Society of Interventional Radiology (SIR)

Released: Mon 22-Dec-2003, 08:10 ET

Highlights from December's Journal of Vascular and Interventional Radiology

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Medical News

KeywordsMEDICAL ADVANCE FOR LOWER GI
HEMORRHAGE UTERINE FIBROIDS
GYNECOLOGISTS**Contact Information***Available for logged-in reporters only***Description**

1) Superselective microcoil embolization for the treatment of lower gastrointestinal hemorrhage is a safe and effective treatment - study results show a far lower complication rate than surgery. 2) Changing trends in gynecologists opinions of UAE.

Newswise — Acute lower gastrointestinal hemorrhage (LGI) is a potentially life threatening condition. Most cases can be managed medically, but 10 – 15 percent require intervention to control the bleeding. The treatment of LGI hemorrhage has traditionally been surgical and the high morbidity and mortality from bowel resection is well-documented – as high as 15–30 percent in emergent operations. These patients are usually an older population at higher surgical risk. Other treatment options also have limitations. Vasopressin infusion, a drug that constricts the blood vessels, is associated with high rates of rebleeding and multiple side effects. In massive hemorrhage, endoscopy is limited because the presence of blood and stool may prevent visualization of the source of bleeding. However, embolization offers a highly effective and minimally invasive treatment to control the hemorrhage. Because interventional radiologists utilize X-ray imaging to guide the catheter inside the body to the site of bleeding, visualization in massive bleeding is not an issue.

Superselective embolization involves mechanically blocking the blood flow to the hemorrhage area through the deployment of tiny coils delivered via a catheter. Interventional radiologists use embolization in many areas of the body to block blood flow to tumors or to treat traumatic or postpartum hemorrhage. The adjacent blood supply from non-target vessels continues to provide sufficient blood flow to the affected organ. However, the weaker blood supply of the LGI tract may predispose the colon to an increased risk of ischemia.

Advances in microcatheter technology such as microcatheters and finer guidewires, coupled with advances in digital fluoroscopic imaging, have resulted in vast improvements in this technique, allowing for superselective -- more precise -- catheterization while preserving the adjacent blood flow to the bowel.

The study reports the authors' experience with superselective embolization and a review of the literature. A combined meta-analysis of 144 superselective microcoil embolizations showed a minimal risk of significant ischemic complication when a modern transcatheter technique is used. The post-embolic infarction rate was estimated as zero percent. In light of these results, and until further studies demonstrate a superior alternative treatment, massive LGI hemorrhage should be treated with attempted superselective microcoil embolization to control bleeding.

→ Changing Trends in Gynecologists Opinions of Uterine Artery Embolization for Fibroids: The Patients Perspective

Interventional radiologists at the Yale University School of Medicine surveyed their uterine artery embolization patients' to determine their gynecologist's opinion of uterine artery embolization (UAE), a relatively new treatment option for uterine fibroids. Traditionally gynecologists have been the providers of treatment for uterine fibroids, however interventional radiologists perform uterine artery embolization, a minimally invasive procedure that blocks the blood flow to the fibroid, causing it to shrink. Twenty-one women who underwent UAE between September 1998 and July 2000 and 21 between July 2000 and April 2002 completed questionnaires. Each woman was asked what her gynecologist's initial opinion was toward UAE, what treatment options were offered, who initiated the

discussion of UAE, and whether she continued to use the same gynecologist after UAE.

As of 2002, more gynecologists had a favorable opinion of UAE and were offering it versus in the first survey time period. In the second survey period, 38 percent were offering UAE as a treatment option, compared with 5 percent in the first survey. Despite this progress, 62 percent of gynecologists still did not offer UAE as a treatment option for fibroids. This is disconcerting because informed consent dictates discussion of all treatment options. The majority of patients whose gynecologists initially opposed UAE did not continue to use that gynecologist, reflecting a similar trend noted two years earlier.

See <http://jvir.org> for abstracts.

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ROCKLAND, Mass.--(BUSINESS WIRE)--Dec. 8, 2003--

Study Indicates Increasing Acceptance by Gynecologists of UFE
as Treatment for Symptomatic Uterine Fibroids

BIOSPHERE MEDICAL, (NASDAQ:BSMD), Approximately 20-40
percent of women 35 years and older experience uterine fibroids
and approximately 50% of African-American women have fibroids.

All too frequently, a woman with symptomatic fibroids faces a
hysterectomy or myomectomy to relieve her symptoms caused by
the fibroids. More recently, a minimally invasive procedure called
uterine fibroid embolization (UFE) has become widely available.
UFE, which is performed by an Interventional Radiologist, is a
uterus-saving procedure using a catheter and an embolic agent,
such as BioSphere Medical's Embosphere(R) Microspheres, to cut
off the blood supply to the fibroid tumors. Symptoms, such as
excessive bleeding and pelvic pain, are relieved as the fibroids
shrink.

Some of the initial challenges to the growth of UFE procedures
have been due to a lack of physician and patient awareness.
However, a recent article published in the December 2003 issue of
the Journal of Vascular and Interventional Radiology reveals a
more positive trend for gynecologists to offer UFE as a first line
therapy for fibroid patients, which is expected to help fuel market
growth of this procedure.

Dr. Michael Tal and Elizabeth Kagan Arleo from the Department of
Diagnostic Radiology, section of Interventional Radiology at Yale
University School of Medicine performed a baseline patient survey
in July 2000 and repeated the survey in April 2002 to investigate if
women believed that their gynecologist were discussing and
offering UFE as a treatment option. Both surveys analyzed the
results of 21 patients, for a total of 42 patients. The survey asked
questions related to their gynecologist's initial opinion of UFE,
which treatment options were offered, who initiated the discussion
of UFE, and whether the patient returned to the same gynecologist
after her UFE. The initial survey in 2000 showed that 76% of their
patient's believed that their gynecologists were opposed or
strongly opposed to UFE as an option. The updated survey in
2002 suggests that only 33% of patients believed that their

INVESTORS

gynecologists were opposed or strongly opposed to UFE. In 2000, the patients in the survey indicated that approximately 5% of gynecologists offered UFE as a treatment option whereas in April 2002, this number increases to 38%.

"UFE is clearly a benefit to women who are suffering the debilitating effects of fibroids, but are hesitant to having major surgery," indicates Dr. Tal. "The process of performing UFE has improved tremendously since 1998; thus, gynecologists should be including UFE in treatment discussions with all fibroid patients. Interventional radiologists have drastically improved patient care, pain management, and patient selection over the course of almost a decade."

Elizabeth Kagan Arleo, fourth year medical student at Yale, comments, "The fact that 62% of gynecologists still do not offer UFE as a treatment option is disconcerting, especially since informed consent dictates discussion of all treatment options available."

Dr. Tal concludes, "Uterine fibroid embolization is a less invasive and safer treatment option in women with symptomatic fibroids than surgery. The trend toward gynecologist acceptance of this safe procedure should only enhance the patient's overall quality of life."

For more information on uterine fibroid embolization, go to www.ask4ufe.com or call toll free: 1-877-ASK-4UFE.

About BioSphere Medical, Inc.

BioSphere Medical, Inc., based in Rockland, Massachusetts, is a medical device company focused on applying our proprietary microsphere technology to medical applications using embolotherapy techniques. Our core technologies, patented bio-engineered polymers and manufacturing methods, are used to produce miniature spherical beads with uniquely beneficial properties for a variety of medical applications. Our principal focus is the treatment of symptomatic uterine fibroids using a procedure called uterine fibroid embolization, or UFE. Our products are already beginning to gain acceptance in this rapidly emerging procedure as well as in a number of other new and established medical treatments. Our strategy is two fold. First, we are seeking to grow the embolotherapy business worldwide, specifically the UFE procedure, by increasing awareness of availability of this procedure. Second, we are seeking to maintain our current technology leadership by the continuous introduction of new products and product improvements, both through internally developed and externally acquired technologies, that improve and broaden the use of embolotherapy techniques.

We have received clearance in a number of countries, including the United States, Canada, Australia and the European Community, which allow us to sell our products for use in general embolization procedures, including uterine fibroid embolization.

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Interventional rads put faith in UFE marketing, research despite skepticism of ob/gyns

6/13/03

By: Tracie L. Thompson

It was less than a decade ago that interventional radiologists reported their first experience with a new procedure for treating noncancerous but symptomatic uterine fibroids, or leiomyomas.

French practitioners had been routinely embolizing the uterine arteries of patients scheduled for myomectomy — seeking to reduce hemorrhage during the subsequent surgery — when they noticed that embolization itself tended to shrink the problematic fibroids. Surgeries were canceled and a less-invasive treatment was born.

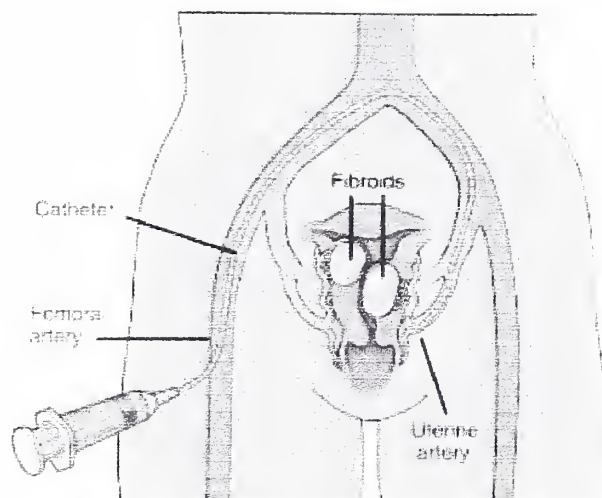
Worldwide as many as 35,000 uterine fibroid embolizations (UFE), also known as uterine artery embolizations (UAE), have been performed since then, and the pace quickens every year. Yet UFE procedures are still dwarfed by long-standing surgical approaches in the U.S., where every year some 200,000 women undergo myomectomy or hysterectomy for fibroids.

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*A basic diagram of a **UFE** procedure. A nick is made in the skin and a catheter is inserted into the femoral artery. The catheter, which is guided through the artery with real-time imaging, releases tris-acryl gelatin microspheres into the blood vessel feeding the fibroid. Image courtesy of SIR.*

Interventional radiologists believe many of these patients would be good candidates for **UFE**, but the situation is déjà vu all over again for radiology. That is, the physicians who "control" most of these patients generally don't refer them out.

The American College of Obstetricians and Gynecologists describes **UFE** as investigational in its most recent practice bulletin on the subject, even though an embolic agent specified for **UFE** was approved by the FDA in November. There are also indications that many gynecologists aren't even mentioning **UFE** to patients as a treatment option — an omission that some observers view as a violation of informed consent (*Clinical Management Guidelines for Obstetrician-Gynecologists*, May 2000, No. 16).

On the other hand, **UFE** is a relatively new procedure. So until recently, clinical studies of its performance have been inherently small and sometimes unflattering.

"I think there is valid scientific caution on the part of gynecologists," said Dr. Evan Myers, an associate professor of obstetrics and gynecology at Duke University Medical Center in Durham, NC, and a leading public health expert on fibroids.

"But there's always a bit of a turf battle that goes on," Myers said. "This is not the first, and not the last time that a new specialty has come out with a procedure or treatment in an area that has traditionally been that of another specialty."

The resistance among gynecologists has already spawned a mini-revolution in radiology practice, inspiring more interventionalists to obtain hospital admitting privileges or develop clinics so they can treat the many **UFE** patients who self-refer.

"It has basically forced us into a situation of providing a full clinical

service," said Dr. J. Mark Ryan, an interventional radiologist at Duke. "We now have gone back to our roots of being real clinical doctors who do ward rounds."

In a presentation at the 2003 Society of Interventional Radiology (SIR) meeting in Salt Lake City, Ryan described his department's relationship with the ob/gyns as "acrimonious." As a result, his team has developed and implemented their own post-UFE pain management protocol without any input from gynecological colleagues (*Radiology*, August 2002, Vol.224:2, pp.610-613).

"(UFE) allowed us to develop an office practice with consultations and see patients outside of the hospital, which we hadn't done before," said Dr. Neal Joseph, director of the two-year-old South Florida Fibroid Center in Hollywood. "Now, in addition to seeing several fibroid patients every office day, we're seeing peripheral vascular patients, renal patients, oncologic patients, aortic stent graft patients – all for consultations."

Encouraged by the success to date and the substantial upside potential of UFE, the interventional radiology community is working to win more hearts, minds, and patients. Major initiatives include research that will hopefully sway gynecologists or at least negate their objections, national information campaigns to educate physicians and the public about the procedure, and local direct-to-consumer marketing by individual practitioners and radiology groups.

Quiet epidemic

A major reason for the successful consumer marketing of UFE is that so many patients are suffering immensely from fibroid symptoms. These include pain and very heavy bleeding that can cause anemia and keep women from work and other activities. Initial treatment generally involves oral contraceptives or non-steroidal painkillers, although these are often insufficient.

Interestingly, although fibroids are by definition a problem of the childbearing years, removing the uterus is the most common surgical solution. Fewer than 40,000 myomectomies occur each year in the U.S., compared to the 150,000 or more hysterectomies performed annually for the treatment of fibroid symptoms.

In fact, U.S. hysterectomy rates have declined only a little over the last two decades, and remain three times higher than rates in Australia and western Europe, according to an analysis published last year in the American College of Obstetrics and Gynecology's peer-reviewed journal (*Obstetrics & Gynecology*, February 2002, Vol. 99:2, pp. 229-234).

"The drivers for innovation tend to be either industry or physician groups," noted gynecologist and researcher Myers. "Hysterectomy cures the problem, so there hasn't been a huge demand, at least from physicians, for alternative treatments."

At the same time, myomectomy has been far from definitive. Unlike UFE, which is designed to cut off the blood supply to all fibroids, surgeons confronted with multiple fibroids at myomectomy must choose which few to tackle. Interventional radiologists say that many of their UFE patients have previously undergone myomectomy.

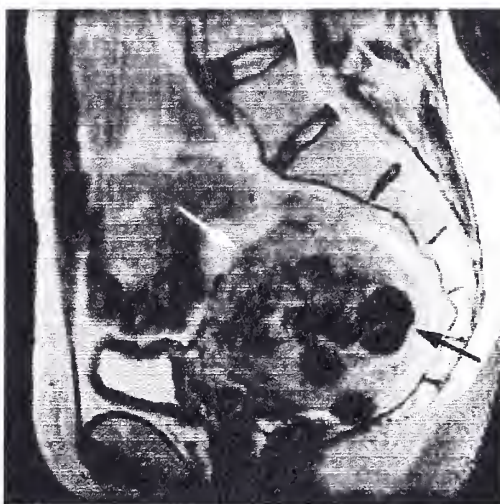
"What we see very often is that the fibroids rapidly go back," says Dr. Steven Janney Smith, director of interventional radiology at LaGrange Hospital near Chicago. "It almost seems like when you take fibroids out with myomectomy, you just make more room for the little fibroids."



This pre-embolization, sagittal T1-weighted midline MR depicts an enlarged uterus with multiple fibroids highlighted by white arrows. The black arrow points out the uterus impinging anteriorly on the bladder neck. Image courtesy of Dr. Steven Janney Smith.

Many myomectomy patients end up having a hysterectomy. But interventional radiologists suggest that gynecologists may have underestimated the number of patients who want to preserve their fertility, or who have a cultural or personal aversion to hysterectomy.

"What I've heard many, many times is, 'I just don't want to lose my uterus. To me it would feel like a castration,'" Ryan said.



The same patient six months after the UFE procedure. This sagittal, T1-weighted midline MR image shows a 50% decrease in the size of the uterus (white arrow). The fibroids have

low signal (black arrow), consistent with devascularization. The patient reported complete relief of symptoms. Image courtesy of Dr. Steven Janney Smith.

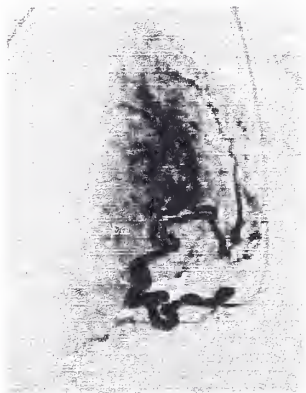
Patients are also self-referring for the other benefits of **UFE**, interventionalists said. As with most interventional radiology procedures, **UFE** is less invasive than the surgical alternatives. A catheter is inserted into the femoral artery and is threaded to the uterine arteries, where embolizing particles of plastic or gelatin are released. Hospitalization is usually one night.

After **UFE** most women can resume normal activity within a week, a shorter time than some myomectomy approaches and definitely shorter than the standard six-week recovery after hysterectomy. The shorter recovery time is appealing for working women and those with families.

Physician shift

Given the pokey evolution of gynecology's fibroid treatments, it's probably not surprising that gynecologists have been slow to even acknowledge the availability of **UFE**. But change is occurring.

After interventional radiologists at Yale University in New Haven, CT, began offering **UFE** in 1998, they started tracking gynecologists' opinion of the procedure by asking patients about the advice they received. Among women who underwent **UFE** at Yale between 1998 and mid-2000, only 10% had learned about the procedure from their gynecologists.



Pre-UFE angiogram with catheter insertion. Contrast highlights fibroids. Image courtesy of Dr. Neal Joseph, Radiology Associates of Hollywood, FL.

By mid-2000 to 2002, some 43% of the patients treated had heard about **UFE** from their gynecologists. But that increase doesn't placate the researcher who presented the latest findings to the Society of Interventional Radiology.

| "A majority of gynecologists still are not offering uterine fibroid

embolization as an option," said Elizabeth K. Arleo, a third-year Yale medical student. "It's disconcerting, because informed consent dictates that all possible treatment options should be mentioned."



The post-UFE image shows arteries occluded for a reduction in blood flow to the fibroids. Image courtesy of Dr. Neal Joseph, Radiology Associates of Hollywood, FL.

Financial self-interest is the driving issue, contends Yale interventionalist Dr. Michael Tal. "The obstetrics is not as lucrative and there's a lot of malpractice (insurance costs), so hysterectomy is one of the main sources of income for gynecologists."

Whatever self-interest they may have, gynecologists are changing their stated position on **UFE**. Only 33% of the gynecologists described in the latest Yale survey were opposed to **UFE** when it was raised as a treatment option, compared to 76% two years earlier.

Interestingly, gynecologists may take a financial hit if they oppose **UFE**: The research also found that patients who underwent the procedure despite their gynecologist's opposition were very unlikely to see that gynecologist again.

Patients first

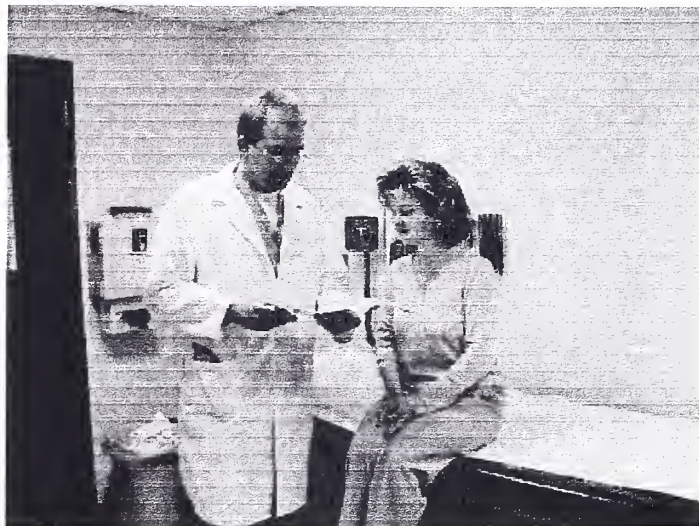
The evolving opinions of gynecologists probably reflect their increasing familiarity with **UFE**, both from national and local sources, Tal said. There have been more journal articles and news reports, and Tal has spoken directly to gynecology groups about **UFE**.

"Initially, the patients that you will get based on those presentations are the patients that nobody wants to operate on," Tal said, citing patients with HIV, hepatitis, obesity, and other comorbidities. Still, "every patient is a way to capitalize on building a relationship with that specific gynecologist."

So with every case, Tal sends the gynecologist copies of all pre- and post-procedure clinical notes. "The key thing in building a **UFE** practice, in my opinion, is to take responsibility for the patient before, during, and after the procedure, and, while doing this, maintain a positive and open communication with the gynecologist," he said.

Even if interventional radiologists have initially taken on new clinical responsibilities because gynecologists refused to work with them, continuing with this approach seems logical and appropriate.

"A model where the gynecologist refers the patient to the IR -- who then does the procedure and the gynecologist then handles all the problems afterward -- isn't going to be very attractive," said gynecologist Myers.



*Getting back to basics: Dr. Michael Tal steps out of the interventional suite to talk with a patient about her **UFE** options. Often a woman's ob/gyn won't even entertain the subject, so it may be up to the interventional radiologist to take over. Image courtesy of Dr. Michael Tal.*

Interventionalist Smith agreed: "Why should I make them admit the patient and do all this if I'm getting paid to do the procedure? It's not fair to them."

Total responsibility for the patient also empowers interventionalists to provide the kind of service that generates good buzz.

"Making sure there are no stones left unturned, making sure that you are treating the patient for post-procedural pain adequately -- basically making a good experience for patients," said Ryan. "I think that has been extremely important."

Consumer marketing

Attention to detail does more than generate word-of-mouth business, Ryan says. Women also share their experiences in Internet health chat rooms that spread the word much farther and wider.

In fact, the Internet appears to be critical in enabling **UFE** to avoid the fate of other new procedures that challenged entrenched approaches. "Women find out information on the Internet and they know what they want," said Tal. "So the gynecologists have to, and do, adapt to that."

Interventionalists also credit the Web sites developed for their practice groups with bringing in numerous self-referred patients. "Without it I don't know how we would have ever gotten started, since right out of the box we were kind of viewed as a threat to the livelihood of

gynecologists," said Smith.

As a new marketing tool for doctors, the Internet also presents some headaches. For instance, Smith was somewhat chagrined when the Web site developer he hired selected DrFibroid.com as the Internet address. "It sounds like I'm a used-car salesman," he complained. But Smith kept the name because at that point, he didn't know that he could choose another.

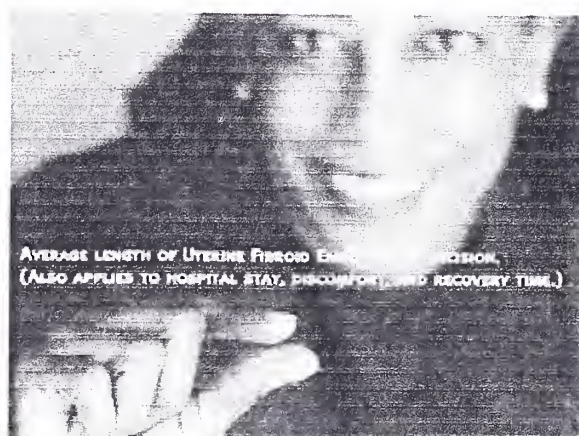


FIGURE 1. Advertisement for uterine fibroid embolization.

One of the most significant developments in uterine fibroid treatments is also one of the smallest. Uterine Fibroid Embolization (UFE) is giving women an important, minimally invasive treatment option to hysterectomy and other invasive surgeries. With less risk and less pain, UFE is performed by interventional

Radiologists - doctors who specialize in targeted, image-guided treatment. By blocking the blood flow to the fibroids and causing them to shrink, the procedure is approximately 60% successful at alleviating the heavy bleeding and painful periods often associated with them. To learn more, consult your physician or visit www.uterinefibroids.org.

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The SIR advertising campaign, marketing UFE directly to patients, generated a significant increase in the number of procedures performed. Image courtesy of SIR.

Other approaches that interventionalists have used to reach patients include speaking to women's groups and inviting local television or newspaper reporters to see a procedure and interview previous patients.

Then there is the marketing used by Joseph for the opening of the South Florida Fibroid Center in 2000. With help from a consultant who had promoted the University of Miami's medical facilities, the fibroid center ran advertisements in major daily newspapers, on cable television, and on two radio stations whose listeners matched the demographics of fibroid patients.

The two-month ad campaign worked so well -- especially the radio spots, which generated 90% of the self-referrals, Joseph said -- that the center did it again a year later.

"We already had a good baseline, but it gave us another boost of patients," said Joseph, who also had anecdotal evidence that his 30-second descriptions of fibroid symptoms and treatment were being heard during drive time. "I'd come to work and everybody was saying, 'Oh, I heard you on the radio.'"

The South Florida Fibroid Center is now handling 20 to 25 embolizations a month. Joseph says that results have also influenced his colleagues at [Radiology Associates of Hollywood](#). "It's just got us into the habit of marketing ourselves and our practice both to physicians and to the public," he said.

National news

In addition to the marketing by individual UFE practitioners, SIR recently completed a yearlong public information campaign that included ads in *Ebony* magazine, the *Journal of Family Practice* and *Annals of Internal Medicine*, and dissemination of video and print press releases and public service announcements.

The campaign generated significant increases in traffic to SIR's call center and Web site: Phone inquiries went up from 45 to 200 per month, and hits on the Web site's UFE "physician finder" went from 25-33 per day to as high as 81 in one day.

Demand for SIR's information has slowed with the conclusion of its campaign, although the society continues to provide patient and physician "Grand Rounds" information both on its Web site and as handouts for use by its 3,000 members.

The education effort has also been picked up by BioSphere Medical, a Rockland, MA, company that received FDA approval of its acrylic copolymer embolizing beads in November. BioSphere is now advertising a toll-free hotline (1-877-ASK-4UFE) and Web site ([www.ASK4UFE](#)) through the *New York Times* and the *Wall Street Journal*.

But mass marketing doesn't always fit comfortably with medicine.

"The problem with any kind of direct-to-patient marketing (by physicians) is there's no real oversight of the validity of claims," Myers said. "Historically, new innovations tend to get marketed very aggressively, and gynecologists have been guilty of that as well with various laparoscopic procedures."

Judging UFE

Interventional radiologists agree that their procedure should be validated through traditional scientific scrutiny, although many argue that the medical literature already makes an excellent case for UFE's safety and efficacy. After all, embolization of the uterine arteries has been performed for more than 25 years to stem postpartum hemorrhage, with studies showing successful treatment and subsequent pregnancies among the patients.

SIR recommends providing referring physicians with studies published in their specialty journals, such as the series of reports in *Fertility and Sterility* on the Ontario Uterine Fibroid Embolization Trial, a prospective

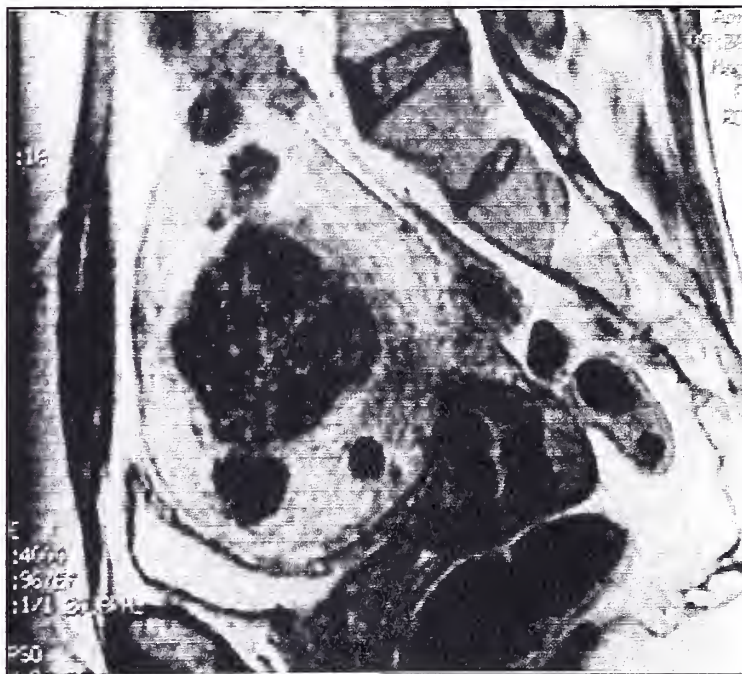
multicenter study of 555 UFE patients.

Another popular citation is an article in *Obstetrics and Gynecology* by Dr. James Spies and colleagues at Georgetown University in Washington, DC. It reported on 400 consecutive patients who underwent embolization, with serious complications for only 1.25% and a 5% overall periprocedural morbidity rate (July 2001, Vol. 98:1, pp. 29-34).

Other articles have reflected less favorably on UFE, including a UCLA study that found that women were more likely to need further invasive treatment after UFE than after myomectomy (*Obstetrics and Gynecology*, November 2002, Vol. 100:5, part 1, pp. 864-868).

Thus, many UFE providers are participating in further research to confirm their perception of the procedure. Foremost among these is the FIBROID registry spearheaded by SIR's Cardiovascular and Interventional Radiology Research and Education Foundation (CIRREF). This registry now includes data on more than 3,000 patients treated at dozens of sites around the world.

In a talk at the 2003 SIR conference, Dr. Robert Worthington-Kirsch from the CIRREF FIBROID Registry Steering Committee shared the latest data on patient demographics and procedure techniques. Boston Scientific of Natick, MA, and Biosphere provided research funds for the multicenter registry. Both companies manufacture embolic microspheres used in UFE.



This pre-UFE, sagittal FSE MR image depicts a large submucosal fibroid and several small intramural fibroids. Image courtesy of Dr. J. Mark Ryan.

"As of August 31, 2002, we have 2,605 cases logged," Worthington-Kirsch said. "Of those 2,605 patients, 2,471 have given consent for long-term follow-up, and 2,300 cases were available for analysis."

Registry enrollment closed after the first of January with somewhat over 13,000 patients enrolled. Data has been provided from 58 sites, 52 in the U.S., four in Canada, one in the U.K., and one in Hong Kong."

The mean age of the women undergoing **UFE** was 43.4 with Caucasians and African-Americans making up the bulk of the patient population. Comorbidities included obesity, smoking hypertension, and diabetes. In terms of reproductive history, just under half had never had a child, he said.

"Just over half the patients were evaluated by MRI, and half the patients were evaluated by either transabdominal or transvaginal ultrasound. The mean uterine volume was just under 1,300 cc with a reasonable spread. Half the patients had one or two fibroids; about a quarter of the patients had five or more fibroids," Worthington-Kirsch said. The majority of patients (85%) complained of menorrhagia. Other symptoms included bulk or pressure and pain.



This sagittal FSE MR image, one-year post-UFE, shows a marked reduction in uterine volume and almost complete shrinkage of the submucosal fibroid, as well as a decrease in the size of intramural fibroids. Image courtesy of Dr. J. Mark Ryan.

In terms of technique, the primary embolic agent used was calibrated microspheres in just under 75% of the patients, he reported. In just over half the patients, microcatheters were used with an average of about 1.2 catheters per case.

"The mean procedure time was about 55 minutes; the mean fluoroscopy time was 16.3 minutes, and this agrees with other procedures of similar difficulty and complexity," Worthington-Kirsch said. "An average of 64 angiographic images were obtained. The overall technical success was 98%, with both uterine arteries embolized. Just about everybody received (intravenous) conscious sedation during the procedure and then most received PCA (patient-controlled analgesia) narcotics afterward for pain management." The

average hospital stay was 1.4 days.

The principal investigator for the FIBROID registry is Duke gynecologist and researcher Myers. He says the database will enable some good conclusions about the safety of **UFE**, as a start. But it won't necessarily enable comparisons with other fibroid treatments.

Myers summarized the problem as lead author of a 2001 [report](#) by the U.S. Agency for Healthcare Research and Quality on management of uterine fibroids: "In general, there was a remarkable lack of high-quality evidence supporting the effectiveness of most interventions for symptomatic fibroids."

Still, winning over gynecologists will probably require radiologists to demonstrate their initiative as researchers as well as clinicians. "I think if there was good data that this was equivalent to myomectomy, it would be harder for there to be resistance," Myers said.

Duke's Ryan is among the interventional radiologists looking to do a head-to-head trial, assuming that gynecologists will participate after he publicly criticized their attitude toward **UFE**.

"You know Osama bin Laden? Well, I came next on the list, pretty much," said Ryan of the reaction he received. "But things have evolved, and there's been generation of mutual respect and greater appreciation of what we as interventional radiologists do."

By [Tracie L. Thompson](#)
AuntMinnie.com contributing writer
June 13, 2003

Additional reporting by Shalmali Pal.

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